Official Title:	**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**
NCT Number:	NCT03185013
Document Dates:	Protocol Version 5.0: 20 November 2019 Protocol Version 4.0: 29 March 2018 Protocol Version 3.0: 28 September 2016 Protocol Version 2.1: 10 June 2016 Protocol Version 2.0: 06 June 2016

16.1.1 Protocol and Protocol Amendments

This section includes the following:

Protocol version 2.0, dated 06Jun2016

Protocol version 2.1, dated 10Jun2016

Protocol version 3.0, dated 23Sept2016

Protocol version 4.0, dated 29Mar2018

Protocol version 5.0, dated 20Nov2019

Protocol Administrative Memo 1, dated 10Sept2018

Protocol Administrative Memo 2, dated 29Apr2019

Protocol Administrative Memo 3, dated 26Mar2021

HPV-301

REVEAL I Trial

(Randomized Evaluation of VGX-3100X and Electroporation for the Treatment of Cervical HSIL)

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100X 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

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 2.0

06 June 2016

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100X 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

Short Title:	Randomized Evaluation of VGX-3100X and Electroporation for the treatment of Cervical HSIL (REVEAL I)
Biological Product:	VGX-3100X
Protocol Number:	HPV-301
Sponsor:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462
Principal Investigator:	[redacted], M.D., M.S. [redacted] Rutgers New Jersey Medical School 185 S. Orange Ave., MSB E-506 Newark, NJ 07103
Medical Monitor:	[redacted], M.D., Ph.D. [redacted] Inovio Pharmaceuticals, Inc.

SUMMARY OF CHANGES

The following is a list of significant protocol changes from HPV-301 protocol version 1.0 dated 26 Apr 2016 to HPV-301 protocol version 2.0 dated 06 June 2016. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol.

1. Added rationale for selection of non-frozen formulation for phase 3 study
2. Added additional background information to Section 2 Study Design
3. Clarified inclusion and exclusion criteria
4. Administrative changes made throughout the protocol for clarification

PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Investigator below constitute his/her approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, ICH-GCP guidelines, local legal and regulatory requirements as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____

Investigator – Signature Date (DD/MMM/YYYY)

_____

Investigator – Printed Name

Site Number: _____

Site Name: _____

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I LIST OF ABBREVIATIONS

AE	Adverse Event
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation with CELLECTRA™ 5PSP
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV 16/18	HPV-16 and/or HPV-18
IC	Intracavitary

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LSIL	Low Grade Squamous Intraepithelial Lesion
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SDC	Subject Diary Card
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

II CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100X 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)[1] of the Cervix	
Estimated Number of Study Centers and Countries/Regions: Approximately 100 Sites in up to 25 Countries	
Study Phase: 3	
Primary Hypothesis: Three 6 mg doses of VGX-3100X (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL[Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3] of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit	
Study Drug Dose	6 mg (1 ml)
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device
Schedule	Day 0, Week 4, and Week 12 study visits
No. of Subjects	Approximately 165 subjects will be randomized in a 2:1 ratio to receive VGX-3100X or placebo
Study Duration	88 weeks
Primary Objective	Determine the efficacy of VGX-3100X compared with placebo with respect to **combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18**
Primary Endpoint	Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsy or excisional treatment) and **no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples** by type specific HPV testing at Week 36 visit

Secondary Objectives	**Associated Secondary Endpoints**
1. Evaluate **the safety and tolerability** of VGX-3100X delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)

[1] Terminology based on 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP)

Secondary Objectives	Associated Secondary Endpoints
	1b. Incidence and severity of serious adverse events (SAE) and Unanticipated [Serious] Adverse Device Effects (UADE) for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2. Determine the efficacy of VGX-3100X compared with placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3. Determine the efficacy of VGX-3100X compared with placebo as measured by **virologic clearance of HPV-16 and/or HPV-18**	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples** by type specific HPV testing at Week 36 visit
4. Determine the efficacy of VGX-3100X compared with placebo as measured by **complete histopathologic regression of cervical HSIL to normal**	4. Proportion of subjects with **no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5. Determine the efficacy of VGX-3100X compared with placebo as measured by both **complete histopathologic regression of cervical HSIL to normal and virologic clearance** of HPV-16 and/or HPV-18	5. Proportion of subjects with **no evidence of LSIL or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) **and no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Week 36 visit
6. Determine the efficacy of VGX-3100X compared with placebo as measured by **histopathologic non-progression**	6. Proportion of subjects with **no progression of cervical HSIL** from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7. Determine the humoral and cellular immune response following administration of VGX-3100X compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 7b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 7c. Flow Cytometry response magnitudes at baseline and Week 15 visits

Exploratory Objectives	Associated Exploratory Endpoints
1. Evaluate tissue immune responses to VGX-3100X in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin,

Exploratory Objectives	Associated Exploratory Endpoints
	CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe the clearance of HPV-16 and/or HPV-18 infection from anatomic locations outside the cervix	2. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from outside the cervix (inclusive of oropharynx, vagina and peri-anus) at Week 36 Visit
3. Evaluate effect of HLA type on efficacy	3. HLA (per-locus and per-allele basis) in conjunction with **histologic regression of cervical HSIL** at Week 36 visit
4. Describe association of previous colposcopy, cytology and HPV testing results with histologic regression at Week 36	4. Colposcopy, cytology, and HPV test results at Weeks 15 and 28 visits in conjunction with histologic regression of cervical HSIL at Week 36 visit
5. Describe the durability of **virologic clearance of HPV-16 and/or HPV-18** for subjects treated with VGX-3100X compared with those treated with placebo	5. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Weeks 62 and 88 visits
6. Describe the patient-reported outcomes for subjects treated with VGX-3100X	6. The following two questionnaires: Short Form Health Survey, version 2 (SF-36v2™) and EQ-5D-5L™ will be self-administered prior to first dose (i.e. Day 0), following each dose, and at Weeks 28, 40 and 88 to measure score(s).

Study Design:

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled Phase 3 study to determine the efficacy, safety, and tolerability of VGX-3100X administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16 and/or HPV-18 (HPV 16/18). The composite primary endpoint is histologic regression of cervical HSIL, and clearance of the underlying HPV 16/18 infection. A sample of approximately 165 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100X or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV 16/18 clears is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization.

To be eligible for the study, women age 18 years and above must consent to participate and have biopsy/biopsies of the cervical lesion(s) at the time of screening. The biopsy slides are sent to a Pathology Adjudication Committee (PAC) in a blinded manner to establish the presence of

cervical HSIL (CIN2, CIN3) prior to enrollment. Subjects must also have a cervical specimen test positive for HPV 16/18 by Cobas® HPV test to be eligible for participation in the study.

All eligible subjects will receive three doses of VGX-3100X or placebo administered IM followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment is administered on Day 0, the second at Week 4, and the third (final) study treatment is administered at Week 12. The first dose is administered as soon as possible following confirmation of the cervical HSIL diagnosis and cervical sample positive for HPV 16/18 but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening.

Subjects are randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category (≤25 vs. >25 kg/m^2), and (c) age category (<25 years vs. ≥25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The long term follow up plan following the Week 36 efficacy assessment will include safety, cytology and HPV testing for a period of approximately 1 year (Week 88).

Efficacy: Visualization of a normal appearing cervix by colposcopy and cytology are insufficient evidence to confirm disease regression. Therefore, disease regression will be based on histopathological assessment, which is considered the definitive method for diagnosis. Subjects will also be assessed by colposcopy, cytology, HPV testing at screening, Day 0, and Weeks 15, 28, 36, 62 and 88. Digital photographs of the cervix will be also used to document colposcopic exam findings.

Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (i.e. loop electrosurgical excision procedure (LEEP), large loop excision of transformation zone (LLETZ), cold knife conization (CKC)) or by biopsy (4 Quadrant Biopsy or 4 Quadrant Biopsy with Endocervical Curettage (ECC)) based upon the assessment at Week 28 of cytology, High Risk (HR) HPV status, and colposcopic findings (see Tables 4 and 5, for Minimally Required Procedures).

Safety: All subjects will be followed for 88 weeks.
Subjects will be monitored for:

1) Local and systemic events for 7 days following each investigational treatment as noted on a Subject Diary Card (SDC);
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

Data Safety & Monitoring Board (DSMB): The DSMB will meet quarterly to review unblinded safety data and histopathologic regression results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with histopathologic regression in the VGX-3100X group is unacceptably low compared to the placebo group. No formal interim analysis will be performed.

Immunogenicity: Humoral and cell mediated immune responses in response to VGX-3100X treatment may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed

for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

Virology: Cervical cytology samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 28, 36, 62, and 88 by Cobas® HPV test. Additionally, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected to test for the presence of HPV 16/18. Vaginal, oropharyngeal and peri-anal samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 36, and 88.

HLA typing: The relationship between subject HLA types and efficacy responses will be explored using available PBMC sample collected for immunogenicity analysis.

Study Population:

Inclusion Criteria:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Has satisfactory colposcopy, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Must have a cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Must have a cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) Women of Child Bearing Potential (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).

- Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
- Intrauterine device or intrauterine system
- Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject

11. Has normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

Exclusion Criteria:

1. Has microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose(i.e. Day 0);
3. Has cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
4. Has history of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
5. Has treatment for cervical HSIL or genital warts within 4 weeks prior to screening;
6. Is pregnant, breastfeeding or considering becoming pregnant during the study;
7. Has history of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
8. Has presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the investigator;
9. Has immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results;
10. Has received any non-study, non-live vaccine within 2 weeks of Day 0;
11. Has received any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
12. Has current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

13. Has malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
14. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
15. Has history of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
16. Has sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
17. Has resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
18. Has prior major surgery within 4 weeks of Day 0;
19. Has participated in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
20. Has less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
21. Has tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
22. Has cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
23. Has metal implants or implantable medical device within the electroporation area;
24. Has active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
25. Is a prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
26. Is an active military service personnel;
27. Is a study-related staff or family member of study-related staff;
28. Has any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Table 1: Schedule of Events

Tests	Screening (-10 wks to -1 Day)	Weeks											
		Day 0	8-14 days post Day 0 Phone Call	4 (± 4 days)	8-14 days post Wk 4 Phone Call	12 (± 4 days)	8-14 days post Wk 12 Phone Call	15 (± 1 week)	28 (± 1 week)	36 (± 1 week)	40 (± 2 weeks) Phone call	62 (± 2 weeks)	88 (± 2 weeks)
Informed consent	X												
Medical History	X												
Demographics	X												
Socio-behavioral[a]	X									X			X
Inclusion / Exclusion	X	X											
Randomization		X											
Physical examination[b]	X	X		X		X		X	X	X		X	X
Vital signs	X[c]	X		X		X		X	X	X		X	X
Screening safety[d]	X												
Pregnancy Test[e]	X	X		X		X		X	X	X		X	X
HIV Testing by ELISA	X												
Blood immunologic samples[f]	X	X						X[g]		X			X
ThinPrep™ [h,i]	X	X						X	X	X		X	X
Cervical Digene swabs[i,j]	X	X						X	X	X			X
Colposcopy, lesion photography[k]	X[l]	X						X	X	X		X	X
Ectocervical biopsy[m]	X									X[n]			
Surgical excision[m]										X[n]			
OP[o], vaginal, anal swabs		X						X		X			X
Inject VGX-3100X/Placebo		X		X		X							
Post treatment assessment		X	X	X	X	X	X[p]						
Distribute SDC		X		X		X							
Review SDC			X		X		X[p]						
PROs		X	X		X		X[p]		X[q]		X [q]		X

[a] Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

[b] Full physical examination (PE) mandatory at screening and study discharge (Wk 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

[c] Screening vital signs must include a measured height and weight and calculated BMI;

[d] Screening 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 30 days prior to dose administration on Day 0;

[e] Negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

[f] At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum per time point (a total of at least 68 mL of whole blood and 8 ml serum should be collected prior to dosing on Day 0). HLA testing will performed once from an existing PBMC sample;

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

[i] Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

[j] Collected prior to the ThinPrep™ sample;

[k] Photographs of the cervix and the associated lesion must be collected prior to and after biopsies and at all colposcopic examinations.;

[l] Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy and corresponding lesion photography is available;

[m] Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (i.e. LEEP, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 5 and 6);

[n] Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from entry and/or Week 36 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing;

[o] Oropharynx (OP) by oral rinse;

[p] Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

[q] PROs to be completed by subject 8-14 days after Week 28 visit and Week 40 phone call

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 HPV INFECTION, CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a HR HPV type [2, 3]. Up to 13000 women in the US alone are diagnosed with cervical cancer each year, which leads to an estimated 4120 deaths [4]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two genotypes are estimated to cause about 70% of all cervical cancers [5, 6].

Incident infection by HPV is characterized by ongoing viral replication and shedding and is associated with early histologic changes (grade 1 cervical intraepithelial neoplasia) when the female cervix is infected with HPV. Most cases of genital HPV infection clear spontaneously, but persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions of the cervix, HSIL which is inclusive of grade 2 and 3 cervical intraepithelial neoplasia (CIN2/3) [7]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [8, 9]. The basis for these changes are attributed to the viral proteins E6 and E7. Infected cells produce E6 and E7 constitutively which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia.

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade CIN caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [10]. This means that the large number of women who already have high grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they didn't respond to vaccination, must currently only rely upon surgery and the chance of spontaneous regression to treat their condition and avoid progression to cancer. Furthermore, the number of US-eligible teenagers who complete the prophylactic vaccination series remains low; 39.7% of US girls ages 13-17 completed their prophylactic HPV immunization series in 2014, which leaves a potentially vulnerable, under-protected population [11]. The current approaches to the management of cervical HSIL typically require surgery (i.e. LEEP/LEETZ, laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100X is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

1.1.2 VGX-3100X

VGX-3100X contains the identical plasmids to target HPV-16 E6/E7 and HPV-18 E6/E7 antigens that were included in VGX-3100. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100X and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV 16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV 16/18.

The initial formulation was designated as VGX-3100 (water-for-injection w/1% w/w poly-L-glutamate (WFI/LGS); frozen storage) and has been administered to more than 250 subjects in Phase 1 and Phase 2 clinical trials.VGX-3100X was developed to be a non-frozen formulation using saline sodium citrate (SSC) buffer. VGX-3100X was administered to 116 subjects in a Phase 1 clinical trial, HPV-101. In study HPV-101, three 6 mg doses of VGX-3100X, non-frozen formulation were delivered intramuscularly followed by electroporation with CELLECTRA™ 5P to healthy adults. Based upon interim analysis data at study Week 14, the non-frozen formulation was considered non-inferior to the frozen formulation based upon a 2-fold rise in overall Spot Forming Units (SPU) to the antigens encoded by the plasmids per 10^6 Peripheral Blood Mononuclear Cells (PBMC) as measured from baseline to Week 14 using the interferon-γ ELISpot assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or 18. The Phase 2b study, HPV-003, enrolled 167 subjects with high grade cervical dysplasia from seven countries and one United States Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, United States and Puerto Rico). Subjects were randomized in a 3:1 ratio to the treatment arm (VGX-3100) or the placebo arm, respectively. All subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histopathology. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit. A secondary endpoint was clearance of HPV 16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol and modified intent to treat analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.3 ELECTROPORATION

VGX-3100X is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [12, 13]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [14, 15]. This technology has been used for more than three decades by molecular biologists for cell transfection and has demonstrated versatility in use, as shown by its functionality in combination with a range of molecules, tissue types, disease indications, and across species [16].

The CELLECTRA™ device developed by Inovio is used for investigational purposes to administer plasmid-based DNA, in both prophylactic and therapeutic settings. Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency, and has demonstrated that the device helps to elicit favorable immunogenicity in several species (e.g., mice, pigs, and rhesus macaques) [17, 18].

VGX-3100 has been administered throughout Phase 1 and Phase 2 investigations with the CELLECTRA™ 2000 device. A next generation device, CELLECTRA™ 5PSP, will be used in Phase 3. Both designs of the CELLECTRA™ device enhance the intracellular uptake of VGX-3100X by the delivery of electrical current, and the electrical current delivery and pulse pattern (electroporation) is identical in both designs. CELLECTRA™ 2000 involves a manual injection of VGX-3100X while the CELLECTRA™ 5PSP device will automate the intramuscular delivery of VGX-3100X and delivery of the EP pulses triggered by a single button press. Neither the dosage nor volume of VGX-3100X administered differs between the two devices. Administration of VGX-3100X with the CELLECTRA™ 5PSP also allows selection of the needle array length from 13 to 19 to 25 mm depending on the estimate of the recipient's subcutaneous fat and muscle tissue.

The technology differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design (Table 2) are not significant and do not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, environmental specifications, and sterilization or performance specifications. The material changes are to the outer housing of the device and not to patient-contacting materials.

Table 2. Comparative Device Overview

	CELLECTRA™ 5PSP	CELLECTRA™ 2000
Array Specifications		
Electrode Number and Material (no bore)	5 Stainless steel, 304 electrodes pentagonal arrangement	5 Stainless steel, 304 electrodes pentagonal arrangement
Electrode Length	1.555 ± .020" (39.5mm)	1.555 ± .020" (39.5mm)
Electrode Gauge	22 Gauge (0.0278-0.0280 inch diameter)	21 Gauge (0.028±0.001 inch diameter)
Electrode Trocar Tip	15 ± 2°	15 ± 2°
Array Housing	Bayer Makrolon 2458C and Loctite 3921	GE Plastics (Sabic) Lexan HPS2
Sterilization Method and Sterility Assurance Level (SAL)	Gamma Irradiation- kGy To Be Determined SAL 10^{-6}	Gamma Irradiation 25-40kGy SAL 10^{-6}
VGX-3100(X) IM Injection Method	Automated (Handset mediated)	Manual (needle and syringe)
Injection Needle Material (full bore)	Stainless steel, 304	Stainless steel, 304
Injection Needle Length	2.102 ± .020" (54.4mm)	2.0" hypodermic needle recommended
Injection Needle Gauge	21 Gauge (.03250-0.03200 inch diameter)	21 Gauge
Injection Needle Trocar Tip	15° (double ended)	15° (single ended)
VGX-3100(X) IM Injection Depth	13, 19 and 25mm	13 and 19 mm
VGX-3100(X) IM Injection Volume	1.0±0.1mL	1.0±0.1mL
Electroporation Parameters		
Voltage	40-200 V maximum (varies with subject tissue impedance; 12V for device operation)	40-200 V maximum (varies with subject tissue impedance; 7.2V for device operation)
Pulse Width	52 milliseconds (ms)	52 milliseconds (ms)
Pulse Current	0.5 A; 1.0 A max	0.5 A ; 1.0 A max
Maximum Phase Charge	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses
Frequency	Up to 4 Hz between pulses	Up to 4 Hz between pulses

Benchtop design verification testing and a non-significant risk device functionality study will be completed prior to Phase 3 to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™5PSP device design meeting its safety and performance specifications, and no change to the administration of VGX-3100(X) by electroporation. Inovio's device experience demonstrates that delivery of electroporation pulses into muscle immediately following injection of DNA plasmids is well-tolerated in humans and no significant safety issues have been identified [19-21].

1.1.4 SELECTION OF STUDY DESIGN

This Phase 3 study employs a prospective, randomized, double-blind, placebo controlled study design to further demonstrate the safety and efficacy of VGX-3100X followed by EP in women with

cervical HSIL associated with HPV 16/18. The primary clinical hypothesis is that VGX-3100X is a surgery-sparing, therapeutic option for the treatment of cervical HSIL and the underlying, pathogenic HPV 16/18 infection, which is supported by the findings of the Phase 2b trial. A placebo-controlled study is selected for this trial because it provides scientific rigor to distinguish an effective treatment, particularly in cervical HSIL for which spontaneous regression does occur.

1.2 DOSE AND REGIMEN RATIONALE

A total dose of 6 mg VGX-3100X DNA has been selected for this study based on previous human experience with both VGX-3100 and VGX-3100X, preclinical data with VGX-3100X and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 2) without significant safety issues [19].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a true effect rather than random variation. Adverse events from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in the Phase 2b study. The results obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Table 3. Percent of Protocol HPV-001 subjects responding and average SFU/10^6 PBMC in responders for each antigen by cohort in Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	%Response	AVG	%Response	AVG	%Response	AVG
HPV-16E6	33%	107	50%	243	50%	1341
HPV-16E7	17%	198	50%	104	67%	143
HPV-18E6	50%	359	50%	338	83%	664
HPV-18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

1.3 RISKS/BENEFIT ASSESSMENT

1.3.1 RISKS ASSOCIATED WITH CURRENT THERAPEUTIC OPTIONS

Currently, treatment of women with cervical HSIL usually consists of either surgical removal of the affected tissue by CKC, LEEP, ablative therapy via laser, or cryotherapy. All treatments for cervical

HSIL are associated with a variety of short and long term general and reproductive health risks as listed in Table 4.

Table 4. Risks Associated with Surgical Treatments for Cervical HSIL

Surgical Treatments for cervical HSIL	Risks
CKC LEEP Ablative therapy (Laser or Cryotherapy)	Pain
	Exposure to anesthesia
	Heavy bleeding
	Infection
	Menstruation problems
	Cervical stenosis (can lead to alteration of squamo-columnar junction)
	Shortening of the cervix
	Decreased fertility/difficulty getting pregnant
	Cervical incompetence
	Pre-term birth and related low birth weight
	Incomplete treatment of cervical dysplasia
	Inadequate treatment of an occult early invasive cancer

Adapted from *FAQs Loop Electrosurgical Excision Procedure (LEEP) American College of Obstetricians and Gynecologists (2014) [11]*.

More importantly, none of the currently available surgical treatments for cervical HSIL eradicate the underlying cause of the high grade cervical dysplasia, persistent infection with one or more of the high-risk HPV types, and therefore, leaves patients at risk for recurrent cervical HSIL as well as high grade dysplasia of the vulva and vagina due to the potentially broader infection of the genitourinary area.

Although professional guidelines typically advocate immediate excisional therapy for adults with cervical HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [8]. The risk of a "missed diagnosis" of an occult early invasive cervical cancer exists for all current treatment modalities including surgical and ablative therapies. Furthermore, approximately 17-18% of patients with high grade CIN will experience recurrence of dysplasia following surgical intervention [8], which illustrates that current standard of care for cervical dysplasia requires improvement. The study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult early invasive cervical cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent cervical colposcopy, cytology and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced gynecologists, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

1.3.2 POTENTIAL RISKS OF STUDY PARTICIPATION

A risk associated with VGX-3100X for the treatment of high grade cervical dysplasia are the injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild (e.g. erythema) and limited to a few days in duration at most.

A second risk is the "delay" in "definitive treatment" of the high grade cervical dysplasia and the "missed diagnosis" of an occult early invasive cervical cancer for the VGX-3100X non-responders or placebo recipients, who do not spontaneously regress. This risk is mitigated by careful serial cytology, HPV testing, and colposcopic exams, throughout the course of the study, and the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. Also, only investigators who are experienced in the management of cervical cancer will be chosen, and they will have the option of performing additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression.

A DSMB will also advise the Sponsor if it appears that the frequency of regression in the VGX-3100X group is unacceptably low compared to the placebo group. These measures should minimize the risk - even perhaps below that of standard care - of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. All subjects with suggestion of residual disease will undergo excisional therapy by CKC or LEEP at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Tables 4 & 5) to provide histopathologic confirmation of regression. In the Phase 2b study, the rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

1.3.3 POTENTIAL BENEFITS OF STUDY PARTICIPATION

All currently accepted treatments for high grade cervical dysplasia are surgical procedures (LEEP, CKC, Laser ablation) which are all associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding and/or infection, damage to other organs, shortening and/or deformation of the cervix, pain, etc. Due to the risk of shortening and/or deformation of the cervix there are additional well accepted risks including cervical stenosis, infertility, cervical incompetence, preterm birth, and inability to visualize the transformation zone. Additionally, none of the surgical treatments systemically address the underlying oncogenic root cause, the high risk HPV infection in the lower genital tract, which leaves an underlying risk for further disease manifestations and transmission of HPV. VGX-3100X+ EP is not associated with any of the risks associated with the surgical procedures outlined above (except for pain, which is transient, very quickly-resolving, and restricted to the deltoid/quadriceps treatment site) and has demonstrated the ability to not only eradicate the high grade dysplasia but also the ability to eradicate the underlying HPV infection. Subjects receiving placebo, who represent women of child-bearing potential, may benefit from the opportunity to be closely managed under careful surveillance over the course of this study and those who regress spontaneously will be able to avoid excisional therapy.

2 STUDY DESIGN

This Phase 3 1 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled study to determine the efficacy, safety, and tolerability of VGX-3100X administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV 16/18.

A sample of approximately 165 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100X or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV 16/18 clears is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization.

Subjects will be randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category (≤25 vs. >25 kg/m^2), and (c) age category (<25 years vs. ≥25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of cervical HSIL. Subjects must also have a cervical specimen test positive for HPV 16/18 by Cobas® HPV test to be eligible for participation in the study.

2.1 ENDPOINT ASSESSMENT

In the Phase 2b study, subjects were randomized 3:1 to the VGX-3100 arm or the Placebo arm. All subjects were scheduled to receive treatment on Day 0, Week 4 and Week 12 and undergo repeat cervical biopsy or surgical excision (i.e. LEEP, LLETZ, CKC) of the cervix at Week 36 to assess efficacy. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit, and the secondary endpoint was clearance of HPV 16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less.

The primary endpoint for the Phase 3 study is based upon the results of the Phase 2b study. Given that HPV persistence is an important factor in the clinical progression of dysplasia and also based upon the findings of the secondary objective of the Phase 2b study, the responder definition for the Phase 3 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV 16/18.

The proportion of subjects who achieved this endpoint in the Phase 2b study was 39.5% of VGX-3100 subjects versus 15.4% for placebo, in the modified-intention-to-treat analysis. The composite endpoint of histologic regression and virologic clearance will be primary in the Phase 3 study, and histologic regression endpoint will be a secondary endpoint.

2.1.1 HISTOLOGY ASSESSMENT

Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Digital photographs are also used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression will be is obtained at Week 36 either by excision (i.e. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or by 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings as outlined in Tables 5 and 6 for subjects 25 years and above and below 25 years, respectively.

Table 5. Minimally Required Procedure at Week 36 for subjects age 25 years and above

Age	Clinical and laboratory information at Week 28				Minimally required procedure at Week 36[a]
	Colposcopy		Cytology	HPV 16/18 testing	
	Quality	Finding			
25 and above	NA	NA	HSIL, ASC-H, AGC, Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	positive	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	negative	4Q biopsy and ECC
	unsatisfactory	no lesion	NILM	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

Table 6. Minimally Required Procedure at Week 36 for subjects under 25 years

Age	Clinical and laboratory information at Week 28				Minimally required procedure at Week 36[a]
	Colposcopy		Cytology	HPV 16/18 testing	
	Quality	Finding			
18-24	NA	NA	Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	HSIL, ASC-H, AGC	NA	Tissue Excision
	unsatisfactory	no lesion	NILM, ASC-US, LSIL	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US, HSIL, ASC-H, AGC[b]	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

[b] if cytology result is AGC "favor neoplasia", tissue excision is recommended

2.1.2 VIROLOGIC (HPV) ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 15, 28, 36, 62, and 88. Also, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for testing of HPV 16/18. Vaginal, oropharyngeal and peri-anal samples will be obtained to

characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 36, and 88 to assess virologic response to treatment at sites other than the cervix.

2.1.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 7) for the primary endpoint takes into account both histopathologic regression of cervical HSIL and virologic (HPV-16 and/or HPV-18) clearance from cervical samples since HPV persistence is an important factor in the clinical progression of HSIL. The responder definition also excludes subjects whose cervix is biopsied at any time between their initial biopsy to determine eligibility and the Week 36 endpoint tissue collection. This exclusion is included to reduce the potential for artefactual increases in the treatment effect caused by removal of HSIL tissue and potentially HPV-16/-18 by unplanned interval biopsies. To qualify as a responder, the subject must have: 1) an acceptable histology specimen at Week 36, which is interpretable by the independent PAC, and 2) an acceptable HPV ThinPrep sample at Week 36, with an associated valid HPV-testing result. A responder is defined as a subject with: 1) no histologic evidence of cervical HSIL and 2) no evidence of HPV-16 or HPV-18 at the Week 36 evaluation. Also, to be considered a responder, the subject must not have had an unscheduled cervical tissue sample obtained between study entry and the Week 36 visit. Conversely, any subject with: 1) histologic evidence of cervical HSIL at the Week 36 evaluation, OR 2) evidence of HPV-16 or HPV-18 at the Week 36 visit, OR 3) a cervical tissue sample obtained between study entry and the Week 36 visit will be designated as a non-responder.

Table 7. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 or HPV-18 at Week 36 AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

2.1.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100X treatment may be evaluated in blood samples taken at baseline (both screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC).

Whenever possible, these studies may be performed on tissue sections from the diagnostic screening biopsy (pre-dose) and from tissue obtained post-dose(s) (Week 36).

2.2 TREATMENT PLAN

The three dose regimen of VGX-3100 appeared to be safe and well tolerated in the Phase 2b study, therefore all eligible subjects who consent to participate in the Phase 3 study will receive the same three 6 mg doses of VGX-3100X or placebo administered in 1 mL IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third (final) study treatment will be administered at Week 12 which is consistent with the Phase 2b study. The first study treatment will be given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16/18 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-16/18.

2.3 SAFETY MONITORING PLAN

Although cervical HSIL is thought to require years to progress to cervical cancer, subjects in the Phase 2b study were followed closely throughout. HPV testing (Weeks 14 and 24), cytology (Week 14) and colposcopy (Week 24) were all mandatory during the observation period prior to obtaining tissue for determination of the primary histologic endpoint at Week 36. Investigators were also instructed to perform additional testing (including biopsy) if disease progression was suspected. These instances were infrequent as only 11 unscheduled biopsies were deemed necessary over the course of the Phase 2b study. In addition, the rate at which occult microinvasive cancer was discovered after 36 weeks was less frequent than what is reported in the literature [22]. Both observations would imply that the mandatory monitoring employed in the Phase 2b study was sufficient; however cervical disease will be monitored even more closely in this Phase 3 study. Colposcopy, cytology and HPV testing will be required at 8 to 14 week intervals throughout the observation period leading up to the primary endpoint 36 weeks after the first dose. Although less frequent monitoring may be adequate, the more frequent monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy.

Safety monitoring will include:

- Local and systemic events for 7 days following each treatment as noted on a Subject Diary Card (SDC).
- All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

In the Phase 2b study, the safety profile was carefully evaluated and treatment with VGX-3100 was well-tolerated based on observations through Week 88 in all subjects. The most common adverse events were administration-site reactions, which included pain, tenderness, erythema and swelling, and were generally mild and limited to a few days in duration. Only erythema showed a statistically higher incidence in VGX-3100 (78%) vs placebo (57%) in the 7- and 28-day periods after a dose. One additional AE, sinusitis, was also statistically significantly increased over the course of the entire study period but resolved without sequelae in the VGX-3100 arm compared to the Placebo arm (10% vs. 0%).

As outlined above, safety monitoring and visit frequency has been designed to take into account the potential risk of delay in the usual treatment of the high grade cervical dysplasia and also the potential for a missed diagnosis of an occult early invasive cervical cancer for the VGX-3100X non-responders or placebo recipients, who do not regress. Serial cytology, HPV testing, and colposcopic exams are applied

throughout the course of the study with the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. All subjects with suggestion of residual disease will undergo excisional therapy by LEEP or CKC at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Table 5 and 6) to provide histopathologic confirmation of regression. The use of a 4 quadrant biopsy in Phase 3 is a change from the approach used in Phase 2b to optimize the evaluation of histopathologic regression taking into consideration the inherent limitations of colposcopy and tissue biopsy samples in the absence of visible lesions [23].

In the Phase 2b study, the cervical tissue sample was initially read by a local pathologist and/or central pathology laboratory for rapid local medical management. The definitive histopathologic assessment was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US. Seven reports included the terms '(adeno)squamous cell carcinoma' or the premalignant condition of 'adenocarcinoma in situ' (AIS) in the final Phase 2b study results which included all 88 weeks of follow up. Three of the cases were reported as AIS, (2 VGX-3100, 1 placebo), out of which two cases (1 VGX-3100, 1 placebo) were confirmed as AIS by the PAC. AIS is a pre-invasive glandular lesion which can be difficult to capture on standard of care screening with initial punch biopsy and is more commonly identified by full excision (e.g. LEEP, conization). There were four reports that included the term squamous cell carcinoma, of which two were confirmed by the PAC, both in the VGX-3100 group. The other two cases (1 VGX-3100, 1 placebo) were diagnosed as CIN3 by the PAC. The rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

Importantly, investigators in the Phase 3 study will be chosen only if they are experienced in the management of cervical cancer as was the case in the Phase 2b study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analysis as outlined in Table 6. These measures should minimize the risk of progression of cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. The frequency of close monitoring by experienced investigators should minimize the risk of cancer progression on the study what is expected with standard of care.

2.3.1 DATA SAFETY & MONITORING BOARD (DSMB)

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will be scheduled to meet quarterly. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with regression in the VGX-3100X group is unacceptably low compared to the placebo group. However, no formal interim analysis will be performed.

2.4 LONG TERM FOLLOW UP PLAN

In the Phase 2b study, all subjects were scheduled to be followed for 1 year after the histopathologic assessment for the primary endpoint (to study Week 88). The establishment of efficacy based on

histopathologic evidence dictated the removal of tissue at week 36 by either punch biopsy (ies) or more extensive surgical resection (i.e. LEEP, CKC). Subjects with colposcopic evidence of residual disease were to undergo LEEP/CKC. A higher proportion of patients who received placebo had a LEEP performed than those who received VGX-3100 (Table 8).

Cytology and HPV 16/18 clearance from the cervix was to be assessed at study Weeks 62 and 88 to evaluate for recurrence of dysplasia and HPV infection after removal of tissue at Week 36. Overall, in the phase 2b study, the majority of subjects had improved cytology and had cleared their underlying HPV 16/18 cervical infection by the Week 62 and 88 visits. For Weeks 62 and 88, there were no clinically meaningful differences noted between the subjects who received an excisional treatment (e.g. LEEP, CKC) and those that showed histopathologic regression and therefore only underwent a biopsy, as shown in Table 8 which summarizes the HPV and cytology results following Week 36.

Table 8. HPV-003 HPV and Cytology results at Weeks 36, 62 and 88, mITT population

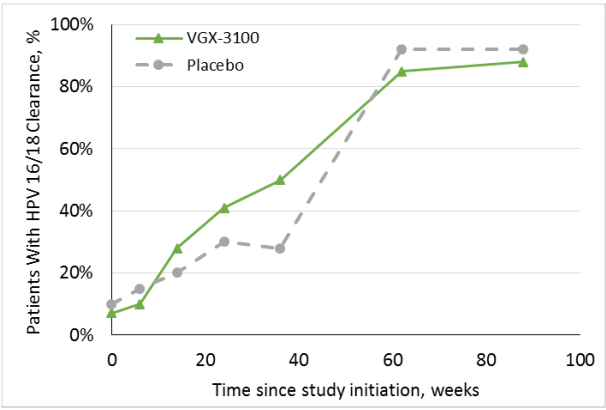
Week	Test[a]	VGX-3100		Placebo	
		LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	100% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89% (42/47)	89% (24/27)	100% (10/10)
88	Pap	96% (52/54)	91% (43/47)	85% (23/26)	100% (11/11)

Abbreviations: NA, not applicable, Pap smear was not done at Week 36
[a] HPV = HPV 16/18 testing; Pap = cytology testing
[b] LEEP or CKC done, at or before the study week as specified
[c] Only biopsy done, at or before the study week as specified

Clearance of HPV 16/18 from the cervix was observed in both treatment groups (Figure 1a) at similar rates until after the second dose when clearance in the VGX-3100 recipients continued to rise while the rate appeared to plateau in the placebo group.

Figure 1. HPV 16/18 Clearance and Pap Smear Findings in Phase 2b mITT Population by Treatment Group

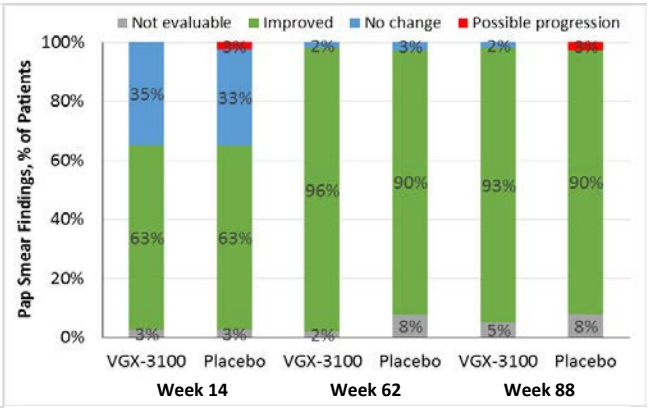
a.



No. of subjects

VGX-3100	123	62	118	116	115	108	103
Placebo	42	26	40	40	40	39	37

b.



No. of subjects

VGX-3100	118	108	103
Placebo	40	39	37

At Week 36, clearance was significantly higher among VGX-3100 subjects that had biopsy (63%) versus LEEP/CKC (41%), which likely reflects the association between clearance of the underlying HPV infection and the likelihood of having signs indicative of regression by colposcopic exam. HPV 16/18 clearance data (mITT population) post-Week 36 are described as follows: HPV 16/18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% (42/51) for VGX-3100 post Biopsy only, 96% (27/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post Biopsy only. HPV 16/18 clearance at Week 88 was 89% (48/54) for VGX-3100 post-LEEP/CKC, 89% (42/47) for VGX-3100 post Biopsy only, 89% (24/27) for Placebo post-LEEP/CKC, and 100% (10/10) for Placebo post Biopsy only.

The majority of subjects had cleared their underlying cervical HPV 16/18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups. Forty-seven of 53 (89%) and 46 of 49 (94%) subjects at Weeks 62 and 88, respectively (mITT population) with histopathologic evidence of CIN2/3 regression (regressors) in the VGX-3100 treatment group experienced HPV 16/18 clearance. Despite the use of therapeutic resection for many VGX-3100 recipients whose CIN2/3 did not regress by Week 36 (non-regressors), HPV 16/18 clearance rates were notably lower (85% at Week 88) compared to regressors.

In the subjects who initially cleared HPV 16/18 by Week 36, only one HPV 16/18 recurrence was identified at the Week 62 and 88 evaluations. Specifically, one subject who had HPV types 16 and 82 and CIN2 at screening, was HPV negative at Week 36, but tested HPV type 16 positive at Week 62, and then cleared HPV 16 at Week 88. The subject showed histopathologic regression at Week 36. No recurrences were identified in the eleven subjects in the placebo group with valid HPV data at Weeks 62 or 88. There were no (0/51) recurrences identified in the VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk as compared to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear cytology results at Week 62 were 93% (52/56) for VGX-3100 post-LEEP/CKC, 100% (51/51) for VGX-3100 post-Biopsy only, 93% (26/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post-Biopsy only. At Week 62, cytopathologic improvement was reported for 104 of

125 (83%) subjects in the VGX-3100 treatment group and 34 of 42 (83%) subjects in the placebo treatment group (mITT population).

There were no instances of possible progression, and all cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. Improvement compared to study entry for Pap smear cytology results at Week 88 were 96% (52/54) for VGX-3100 post-LEEP/CKC, 91% (43/47) for VGX-3100 post-Biopsy only, 85% (23/26) for Placebo post-LEEP/CKC, and 100% (11/11) for Placebo post-Biopsy only. At Week 88, possible progression (atypical glandular cells) was reported in a single Placebo subject in the post-LEEP/CKC group (3%) and no subjects treated with VGX-3100. All other cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. The majority of subjects showed improvement, and there was no meaningful difference between the Week 62 and Week 88 evaluations. These findings support that study subjects had no increased risk of progression based upon cytology as compared to standard of care.

The protocol-specified removal of dysplastic cervical tissue at Week 36 by either method substantially affected the clearance of HPV 16/18 and normalization of cytologic findings as expected, regardless of treatment group (Figure 1a, b). HPV 16/18 clearance rises at a sharp rate after tissue is removed at Week 36 whether the excision is wide (LEEP/CKC) or more limited (biopsy). Notably, the method of tissue collection at the Week 36 endpoint did not appreciably affect the HPV 16/18 clearance rates beyond Week 36 (Table 8). Based upon the Phase 2b results, the risk of progression or recurrence of cervical dysplasia is low and comparable to the rates observed post-LEEP/CKC in clinical practice. The long term follow up planned for this Phase 3 study will include safety, cytology and HPV 16/18 testing at 6 months and also 1 year following the Week 36 histopathologic assessment, which is highly conservative given the expectation that few subjects will have persistent evidence of disease after the removal of tissue at Week 36 which is supported by the findings in the Phase 2b study.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 HYPOTHESIS

Three 6 mg doses of VGX-3100X (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered IM followed by EP with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV 16/18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit.

3.2 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of VGX-3100X compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18	Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in ThinPrep® cervical samples by type specific HPV testing at Week 36 visit

3.3 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Objectives	Associated Endpoints
1. Evaluate the safety and tolerability of VGX-3100X delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit) 1b. Incidence and severity of serious adverse events (SAE) and Unanticipated [Serious] Adverse Device Effects (UADE) for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2. Determine the efficacy of VGX-3100X compared with placebo as measured by histopathologic regression of cervical HSIL	2. Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3. Determine the efficacy of VGX-3100X compared with placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in ThinPrep® cervical samples by type specific HPV testing at Week 36 visit
4. Determine the efficacy of VGX-3100X compared with placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5. Determine the efficacy of VGX-3100X compared with placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6. Determine the efficacy of VGX-3100X compared with placebo as measured by histopathologic non-progression	6. Proportion of subjects with no progression of cervical HSIL from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7. Determine the humoral and cellular immune response following administration of VGX-3100X compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 7b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 7c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.4 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Objectives	Associated Endpoints
1. Evaluate tissue immune responses to VGX-3100X in cervical samples	Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe the clearance of HPV-16 and/or HPV-18 infection from anatomic locations outside the cervix	2. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from outside the cervix (inclusive of oropharynx, vagina and peri-anus) at Week 36 Visit
3. Evaluate effect of HLA type on efficacy	3. HLA (per-locus and per-allele basis) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe association of previous colposcopy, cytology and HPV testing results with histologic regression at Week 36	4. Colposcopy, cytology, and HPV test results at Weeks 15 and 28 visits in conjunction with histologic regression of cervical HSIL at Week 36 visit
5. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100X compared with those treated with placebo	5. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
6. Describe the patient-reported outcomes for subjects treated with VGX-3100X	6. The following two questionnaires; Short Form Health Survey, version 2 (SF-36v2^{TM}) and EQ-5D-5L^{TM} will be self-administered prior to first dose (i.e. Day 0), following each dose, and at Weeks 28, 40 and 88 to measure score(s).

4 SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36
7. Has satisfactory colposcopy, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Must have a cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Must have a cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) WOCBP is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
        - Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
        - Intrauterine device or intrauterine system
        - Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject

11. Has normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from enrollment in the study:

1. Has microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose(i.e. Day 0);
3. Has cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
4. Has history of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
5. Has treatment for cervical HSIL or genital warts within 4 weeks prior to screening;
6. Is pregnant, breastfeeding or considering becoming pregnant during the study;
7. Has history of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
8. Has presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the investigator;
9. Has immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
10. Has received any non-study, non-live vaccine within 2 weeks of Day 0;
11. Has received any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
12. Has current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure;

angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

13. Has malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
14. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
15. Has history of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
16. Has sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
17. Has resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
18. Has prior major surgery within 4 weeks of Day 0;
19. Has participated in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
20. Has less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
21. Has tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
22. Has cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
23. Has metal implants or implantable medical device within the electroporation area;
24. Has active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
25. Is a prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
26. Is an active military service personnel;
27. Is a study-related staff or family member of study-related staff;
28. Has any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests Grade 3 toxicity attributable to the study treatment, the medical monitor and Investigator will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All randomized subjects should be encouraged to complete all study treatments and follow-up visits. A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule for follow-up and treatment of HSIL (CIN2, CIN3), and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

If a subject elects to withdraw from the study (during or after study treatments), she should be encouraged to stay in the study and complete all follow-up visits and procedures. Subjects who are withdrawn from study participation after starting randomized treatment will not be replaced. Reasons for study withdrawal will be recorded in the eCRF and the subject's source document.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/ WITHDRAWAL

The investigator or study coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1 – Safety Parameters.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the CRF:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death of subject
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the CRF. This reason does not allow for

further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.

- Investigator decision to withdraw the subject from participation: Investigator determined a medical need to withdraw the subject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject from participation in the study
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including telephone calls, letter sent by certified mail or equivalent.
- Other: The subject was terminated for a reason other than those listed above, such as the termination of the study by the Sponsor

5 STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The active and placebo formulations to be used in this study are described in Table 9. Both IPs will presented in clear glass cartridges and will be injected intramuscularly.

VGX-3100X and placebo will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 9. Investigational Products

Product	Formulation	Dose
VGX-3100X	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Placebo	150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 BLINDING

This study is double-blinded with blinding maintained throughout the study by use of identical packaging for both the active product and the placebo. There is no difference in appearance for both the active product and the placebo.

The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is essential for proper clinical management of the subject, as judged by the investigator. It is preferred, but not required, that the investigator first contact the Medical Monitor to discuss options before unblinding the subject's treatment assignment. In case of non-emergency, investigator must contact Medical Monitor to discuss the options before unblinding the subject's treatment assignment.

The Sponsor's or designee's pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE, UADE, or AE of interest. No personnel directly involved with the study will be unblinded. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's treatment assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCT

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, double-panel label with tear-off. Both VGX-3100X and placebo labels will include, at minimum, the following information in Table 10:

Table 10. Example Labels for Investigational Product

Cartridges (primary container)	**Pouches** (secondary package)
VGX-3100X or Placebo Insert cap end IM administration Inovio Pharmaceuticals, Inc.	Study ID/Material ID VGX-3100X or Placebo Single-use, 1 mL Storage temperature, expiration date CAUTION: New Drug – Limited by United States Law to Investigation Use Inovio Pharmaceuticals, Inc.

5.4 HANDLING OF INVESTIGATIONAL PRODUCT

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Unless otherwise specified, IP will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Immediately upon arrival, IPs should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition.

Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

5.5 DISPENSING OF INVESTIGATIONAL PRODUCT

It is the responsibility of the Investigator to ensure that the IP is only dispensed to study subjects. It must be dispensed only from official study sites by authorized personnel according to local regulations.

When a subject is eligible for randomization, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration. The pouch must not be discarded until 1) administration is completed and 2) all pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator.

The device user manual and instructions for use will inform clinical personnel about placement of the IP cartridge into the device, as well as the steps for injection and electroporation.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused and/or partially used IP must be returned to Inovio Pharmaceuticals, Inc., or its designee, if not authorized by Inovio Pharmaceuticals, Inc. to be destroyed at the site.

The IP cartridge will be discarded along with the disposable array within a sharp's container at site.

All IP returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor.

If IP(s) are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor

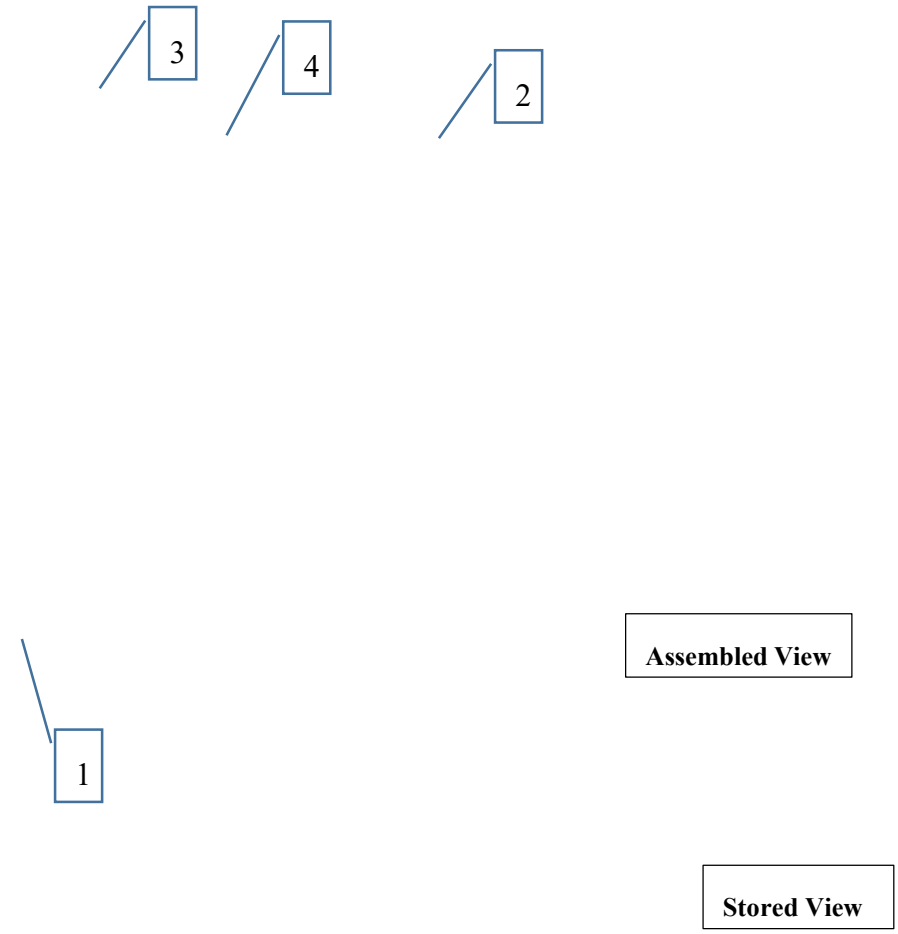
5.8 INVESTIGATIONAL DEVICE

The needle array component of CELLECTRA™ 5PSP device is provided sterile and is intended for single-use. CELLECTRA™ 5PSP device is intended to be used by qualified and trained healthcare professionals in clinical settings. The Investigator for this study will be trained in the use of the device.

CELLECTRA™ 5PSP has 3 main components that are used in conjunction with the drug cartridge (see Figure 2):

1. **Base** – Acts as a docking station for the Handset and as the primary display for entering subject information; must be used with the provided Power Supply
2. **Handset** – Controls delivery of the drug and electrical pulses
3. **Array** (single-use sterile) – Attaches to the Handset and contains the injection needle, electrodes and sensors used for drug delivery and electroporation.
4. **Drug Cartridge** (single-use) – a separate container-closure containing the IP solution. The Cartridge is inserted into the array for administration of the IP.

Figure 2. Components of the CELLECTRA™ 5PSP device and drug cartridge



The CELLECTRA™ 5PSP device has unique features that make using it different from using other injection systems:

1. Each Handset is uniquely paired to a Base. The serial numbers on the bottom of the Base and Handset must match.
2. There is no communication between the Base and Handset when separated; the Handset must be placed onto the Base to share power or data.
3. The Handset has an internal battery that must be charged on the Base before use.
4. Needle depth is selectable on the Handset at the following lengths: 13 mm, 19 mm, or 25 mm. Even though the system provides a needle depth recommendation based on a

Subject's height and weight, the user will be asked to manually enter the needle depth based on the protocol requirements (refer section 5.9), described

5. Injecting the placebo and delivering electrical pulses takes time (usually 10 seconds). The Handset will let you know when treatment is complete.
6. The Subject should be maintained in a safe and secure, braced position due to involuntary muscle spasms that may occur during delivery of the electrical pulses.

Before using the CELLECTRA™ 5PSP device, the Investigator and research staff must be trained by the Inovio Pharmaceuticals Inc. device trainer(s) and be requested to read the entire user manual and complete the Self-Assessment.

5.9 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the device are located in the CELLECTRA™5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training. Training will include review of the entire device user manual and instruction video and hands-on training. After training on the proper use of the CELLECTRA™5PSP device, intended users at each site will be required to demonstrate their competence in its use to Inovio or its designee.

Briefly, the Handset and Array should be prepared according to the instructions in the user manual. Remove the array from its packaging while avoiding contact with the end of the array that attaches to the handset, and insert the drug cartridge into the array with the arrow on the cartridge pointing away from the handset.

Attach the Array to the Handset and set the needle depth on the handset to the longest needle length judged to allow safe injection into the muscle per the investigator's assessment.

The subject must be in a safe and secure, braced position. The subject's body should touch the bed or be braced against the bed or have the study staff performing electroporation or assistant in ~~the~~ position to brace the subject's arm or leg (as appropriate) as the EP is administered. The user will then insert the CELLECTRA™ 5PSP needle array into the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) of the participant in accordance with the CELLECTRA™ 5PSP user's manual instructions. Once triggered by the user, the device will automatically deliver the blinded treatment followed by the EP pulses. The entire treatment period lasts for about 10 seconds.

The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel. Individuals whose credentials do not meet the relevant local requirements may perform the treatment procedure under both of the conditions below:

1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform the procedure.

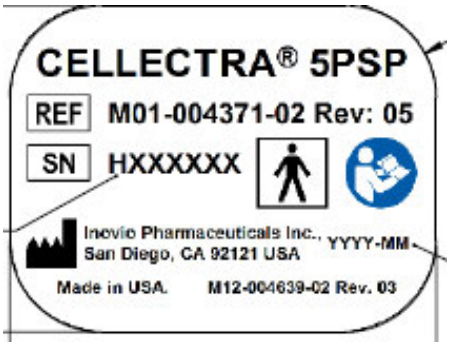
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.10 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

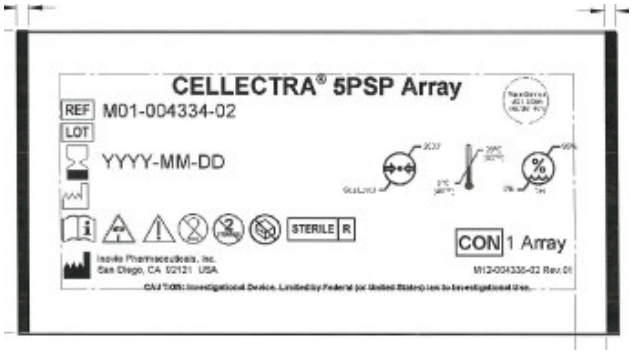
See below Figure 3 for example CELLECTRA™ 5PSP device component labels.

Figure 3. Device Labels (Base, Handset, Array)

BASE



HANDSET



ARRAY

5.11 HANDLING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual.

5.12 INVESTIGATIONAL DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining investigational device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational product. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP serial number, array lot number and the study drug lot number. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.13 RETURN OF INVESTIGATIONAL DEVICES

Upon completion or termination of the study, all investigational devices and unused components must be returned to Inovio Pharmaceuticals, Inc.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by the responsible Study Monitor.

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

After providing informed consent, subject's cervical biopsy tissue samples (e.g., formalin fixed tissue, paraffin-embedded tissue) and/or biopsy slides will be sent to the PAC for review by two study pathologists. Discordant results will be reviewed by a third pathologist to achieve a consensus diagnosis. Subjects must have a diagnosis of histologic HSIL (CIN2 or CIN3) confirmed by the PAC and a screening cervical specimen (i.e. ThinPrep™) test positive for HPV-16 and/or HPV-18 by Cobas® HPV test to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

- Biopsy specimens and colposcopic photographs obtained within 10 weeks prior to Day 0 as part of standard of care before the informed consent may be used as part of the screening and evaluation process.
- If the pathology results of the initial biopsy obtained as part of standard of care are available confirming the presence of HSIL (CIN 2 or CIN 3), those biopsy slides or sample(s) may be sent directly to the PAC for concurrence after the subject has signed the informed consent.
- For those individuals diagnosed with cervical HSIL by a local pathologist, where the initial biopsy slides or tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, colposcopy with cervical photography may be

performed and an additional biopsy sample may be collected during screening at the discretion of the investigator and consent of the subject. The additional biopsy sample may be sent directly to the PAC for review, if allowable per local or institutional guidelines.

The assessments during the screening period will determine the subjects' continued eligibility for the study and also their ability to comply with protocol requirements by completing all assessments.

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to 1 day prior to dosing on Day 0 – except for the safety laboratory collections/assessments, which must be performed within 30 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy with lesion photography and cervical biopsy
- Demographics; including age, and race/ethnicity
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Determination of eligibility per inclusion / exclusion criteria
- Full Physical Examination (including height, weight and BMI measurements)
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 30 days prior to Day 0);
- Urine pregnancy test
- Serology (HIV Antibody) (within 30 days prior to Day 0)
- Whole blood (at least 34 mL) and serum (at least 4 mL) for baseline immunologic assay
- 2 Digene cervical brush samples

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluation will be performed on **Day 0 prior to study treatment:**

- Determination of eligibility per inclusion / exclusion criteria
- Randomization
- Targeted Physical Exam
- Vital signs
- Urine pregnancy test

- Whole blood (at least 34 mL) and serum (at least 4 mL) for baseline immunologic assay (a total of at least 68 mL of whole blood and 8 ml serum should be collected prior to dosing on Day 0)
- Colposcopy with lesion photography
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) sample by oral rinse and vaginal and anal swabs
- Patient-Reported Outcomes (PROs) completion

Study treatment will be administered and the following evaluations will be performed on **Day 0 post-treatment:**

- Post treatment adverse event and injection site reaction assessment within a minimum of 30 minutes after study treatment
- Distribute Subject Diary Card (SDC)
- Download EP data from device

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review Day 0 SDC
    - The subject should submit their SDC (via email, fax, mail) to site personnel prior to the phone visit. If the SDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the SDC should be collected and reviewed at the next in-person study visit. After completing a review of SDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.3 WEEK 4

The following study evaluation will be performed on **Week 4 prior to study treatment (± 4 days):**

- Targeted Physical Exam
- Vital signs
- Urine pregnancy test
- Collect SDC for dose 1

The following study evaluations will be performed **on Week 4 post treatment:**

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment;
- Distribute SDC
- Download EP data from device

6.2.4 8-14 DAYS POST DOSE 2

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review SDC for dose 2
    - The subject should submit their SDC (via email, fax, mail) to site personnel prior to the phone visit. If the SDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the SDC should be collected and reviewed at the next in-person study visit. After completing a review of SDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.5 WEEK 12

The following study evaluation will be performed on **Week 12 prior to study treatment (± 4 days):**

- Targeted Physical Exam
- Vital signs
- Urine pregnancy test
- Collect SDC regarding Dose 2

The following study evaluations will be performed **Week 12 post treatment**:

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment;
- Distribute SDC
- Download EP data from device

6.2.6 8-14 DAYS POST DOSE 3

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review SDC for dose 3
    - The subject should submit their SDC (via email, fax, mail) to site personnel prior to the phone visit. If the SDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the SDC should be collected and reviewed at the next in-person study visit. After completing a review of SDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.7 WEEK 15

The following study evaluations will be performed on **Week 15 ± 1 week:**

- Targeted physical assessment

- Vital signs
- Urine pregnancy test
- Whole blood (at least 51 mL) and serum (at least 4 mL) for immunologic assays
- Post-treatment injection site reaction assessment
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) by oral rinse and vaginal and anal swabs
- Collect SDC
- Colposcopy and lesion photography

6.2.8 WEEK 28

The following study evaluations/actions will be performed on **Week 28 ± 1 weeks:**

- Targeted physical Assessment
- Vital signs
- Urine pregnancy testing
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography to assess for possible disease progression
- PRO to be completed by subject 8-14 days after Week 28 visit

6.2.9 WEEK 36

The following study evaluations will be performed on **Week 36 ± 1 week:**

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Whole blood (at least 34 mL) and serum (at least 4 mL) for immunologic assays
- Urine pregnancy test
- ThinPrepTM sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) by oral rinse and vaginal and anal swabs
- Colposcopy and lesion photography
- Biopsy or surgical excision

The investigator will utilize information collected at Week 28 to determine the appropriate method for obtaining tissue for histopathologic assessment as described in Tables 4 & 5 for minimally required procedure (4 quadrant biopsies, 4 quadrant biopsies and ECC, or excision).

6.2.10 WEEK 40 PHONE CALL

The following study evaluations will be performed on **Week 40 ± 2 weeks** via a phone call:

- Review of histology results as read by PAC from Week 36
- PRO to be completed by subject 8-14 days after Week 40

6.2.11 WEEK 62

The following study evaluations will be performed on **Week 62 ± 2 weeks:**

- Targeted physical assessment
- Vital Signs
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography

6.2.12 WEEK 88

The following study evaluations will be performed on **Week 88 ± 2 weeks:**

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Full Physical Exam
- Vital Signs
- ThinPrep® sample for HPV PCR and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography
- Whole blood (at least 34 mL) and serum (at least 4 mL) for immunologic assays
- Oropharynx (OP) by oral rinse and vaginal and anal swabs
- PRO completion

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified study personnel will

document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a upto two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with [redacted] (e.g., [redacted]). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.3 SAFETY EVALUATIONS

6.3.3.1 Physical Exam

A full physical examination (PE) will be conducted during screening and study discharge. It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

A targeted physical assessment will be performed at other visits as determined by the investigator or directed per subject complaints. The injection site is to be assessed by the study personnel at 30 minutes after each study treatment.

6.3.3.2 Vital Signs

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 Weight and Height

Weight (kg) and height (cm) will be collected at screening in order to calculate the BMI (BMI = kg/m^2).

6.3.3.4 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. The medical history will include a) any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s), and b) if treated previously for CIN, the respective treatment type(s) and date(s).

6.3.3.5 Socio-Behavioral Assessment

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported

recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained.

6.3.3.6 Laboratory Evaluations

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count w/ differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- SGPT (serum glutamic-pyruvic transaminase)/ALT
- BUN (blood urea nitrogen)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- CPK (creatine phosphokinase)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose $\geq$ 1+) a microscopic examination should be performed.

6.3.3.7 Demographics

Demographic information will be collected via self-report (unless noted otherwise), including the following:

- Age (via date of birth)
- Race/ethnicity

6.3.3.8 Urine Pregnancy Testing

For subjects of reproductive potential, a negative spot urine pregnancy test is required prior to each study treatment, colposcopy and surgical excision.

6.3.3.9 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QTcb or QTcf, ST segment, Twave as well as an investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as “clinically significant (CS)” or “not clinically significant (NCS)” by the investigator

6.3.3.10 Subject Post Treatment Assessments

SDC will capture subject reported local and systemic events for 7 days after the study treatment as shown in Appendix A.

The subject will be provided a SDC and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed SDC will be reviewed with the subject and research staff at 8 -14 Days post-dose.

The study staff will review the SDC for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse event accordingly.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a 3-dose series of either 1 ml VGX-3100X or Placebo by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with the CELLECTRA™ 5PSP. Study treatment must not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.4.1 RISKS OF TREATMENT PROCEDURES

Table 11 summarizes reported AEs and potential risk to study treatment.

Table 11. Summary of Reported Adverse Events and Potential Risks or VGX-3100X delivered IM EP with CELLECTRA™ 5PSP

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration

Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury • Disruption of function of implanted electronic medical devices (if CELLECTRA ™ 5PSP device is not used per User Manual) • Exacerbation of unstable cardiac disease • Effects on the fetus and on pregnancy

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO TREATMENT

Subjects may be offered topical anesthetic (i.e. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening will be performed for inclusion into the study as listed in section 6.1.1.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and within minimum of 30 minutes after each study treatment and at 2 to 4 weeks post study treatment visits. They will also be advised to record local and systemic AEs for 7 days on a SDC as shown in Appendix A.

A Medical/Clinical Assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured

from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 12. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, previously-validated patient-reported outcomes (PRO) instruments will be provided to the subjects. PRO questionnaires will include the following, along with the license holder, respective numbers of items and domains, and listed domains:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [24] (See Appendix D for sample questionnaire).
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status via VAS) [25, 26] (see Appendix E for sample questionnaire).

The PRO instruments will be provided to subject and will be instructed to complete the questionnaire at the following time points:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- 8-14 days post dose 2
- 8-14 days post dose 3
- 8 -14 days post Week 28
- 8-14 days post Week 40
- Week 88

Administration of PRO instruments will be performed according to the validated procedure and guidelines of each respective instrument, except for some assessments for exploratory analyses.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 36, 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100X.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine 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). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available

6.11 HLA TYPING

HLA testing will be performed on PBMC from any single blood sample collected for immunogenicity analysis. If the subject has a record of previous high resolution HLA testing and access to the results, then HLA testing is not required.

The DNA extracted from the blood sample will be used to determine if alleles at the MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at the screening, Day 0, Weeks 15, 28, 36, 62, 88 and read in a central laboratory. HPV PCR by Cobas® HPV test will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer at Day 0, Weeks 15, 28 or 36, the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples to eliminate potential interference with the results of HPV testing.

At visits where multiple cervical samples are collected, the two Digene cervical brushes will be collected prior to the ThinPrep™ sample. Details of sample collection and shipment information will be provided in laboratory manual.

6.13 COLPOSCOPY AND CERVICAL BIOPSIES

Colposcopy at screening must be adequate, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected dysplasia. An ECC is not required for study entry. However, if an ECC was done as part of routine care during the screening period, and found to have evidence of cervical HSIL such subject should not be enrolled in the study. Colposcopy is not required to be performed at screening if adequate colposcopy was previously obtained upon collection of initial biopsy. All colposcopies performed after informed consent must be conducted according to the procedures outlined in Appendix C.

Interval colposcopies will be performed at Day 0, Weeks 15, 28, 36, 62, and 88. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

Digital photographs of the cervix will be captured during each colposcopic examination to document the clinical findings. If a biopsy or surgical excision is performed, images of the cervix should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach and 2) the process for uploading the images to a secure server. Additionally, after subject is enrolled if vaginal or vulvar lesion should develop, photograph should be taken to document the clinical exam finding.

6.13.1 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at screening to confirm eligibility. If the criteria outlined in Table 5 or 6 are met, ectocervical biopsies may also be performed at Week 36 to provide tissue for histopathologic assessment of disease regression.

Biopsies should not be performed at any other visit unless there is suspicion of disease progression. Removal of additional tissue by biopsy before Week 36 will bias results toward improvement regardless of whether the subject is in the active or placebo group. The bias introduced will obviously

be more significant for smaller lesions. For this reason, if biopsies are obtained prior to Week 36, the subject will be treated as a non-regressor. Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy prior to Week 36, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.13.2 UNSCHEDULED BIOPSIES

In the event unscheduled biopsy is performed prior to Week 36, subject will be considered as non-responder. The subject will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and Investigator's judgement based on results of histological diagnosis from unscheduled biopsy Additional instructions for collecting ectocervical biopsies are detailed in Appendix C. All biopsy samples/excised tissue will be sent to the PAC for review.

6.14 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

6.15 RESTRICTIONS

6.15.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled otic and ophthalmic corticosteroids are allowed
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine
- Blood thinners/Anticoagulants within 2 weeks of any study treatment

6.15.2 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS:

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy; see Section 7.1.9 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS:

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.2.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.
Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.3 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event

is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.4 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

7.1.5 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported.

The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)

The investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.6 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the investigational device. An AE may also be assessed as not related to the IP and/or the investigational device. Because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the investigational device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event.

7.1.7 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

7.1.8 POST-STUDY REPORTING REQUIREMENTS

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol-required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.9 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor study team and medical monitor within 24 hours after learning of the pregnancy. The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject. Subjects who are not withdrawn will continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF THE COLLECTION AND RECORDING OF SAFETY DATA

Non-serious AEs and SAEs (and UADEs) will be collected for each subject from the time when informed consent is obtained through Week 88.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.

3. Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE (or UADE) occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 EVENTS REQUIRING EXPEDITED REPORTING

Events requiring expedited reporting (ERER) will be defined as related adverse events due to VGX-3100X/placebo delivered with CELLECTRA™ 5PSP that meets any of the following criteria:

- Grade 3 or greater administration site erythema, and/or induration recorded ≥ 2 hours after Study Treatment
- Grade 4 or greater administration site pain, tenderness recorded ≥ 2 hours after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

As per the Toxicity Grade for Healthy Adults and per CTCAE v 4.03. The most severe grade for that particular event is to be documented in the CRFs.

Sites will inform the Sponsor vial email and to designee vial phone or fax of any ERER within 24 hours to discuss whether further dosing should continue by contacting Inovio as follows.

EMAIL: Safety@inovio.com
SAFETY FAX: [redacted] or [redacted]
SAFETY PHONE: [redacted]

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

- If at any time during a study one-third (1/3) or more of the subjects experience an ERER, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB. Only the DSMB may review unblinded data in making their recommendation to the Sponsor regarding continuation of a trial.

- If any SAE (or potentially life-threatening AE), or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study, experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

The sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

8 STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects with a histologic diagnosis of cervical HSIL. The study's primary endpoint is binary: regression to CIN1/normal and clearance of HPV-16 and/or 18 infection from cervical tissue based on tissue collected at Week 36. The primary hypothesis is that VGX-3100X will be superior to placebo regarding the proportion who achieve the primary endpoint. Secondary efficacy analyses involve regression to CIN1/normal, clearance of HPV-16 and/or 18 infection from cervical tissue and non-progression of cervical lesions. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or 18 infection from cervical tissue, clearance of HPV-16 and/or 18 infection from non-cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, and virology and efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized (2 VGX-3100X:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) BMI category ($\leq$25 vs. >25 kg/m^2), and c) age category (<25 years vs. $\geq$25 years). There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The study is double-blinded.

8.3 SAMPLE SIZE/POWER

A sample of 165 subjects will be randomized to receive either 6 mg VGX-3100X or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization. These assumptions are based on the mITT result from the Phase 2 study.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be primary for the analysis of efficacy in this study.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

Subjects who do not complete the study will not be replaced.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment arm for all randomized subjects and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the mITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the mITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible

date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true population probabilities of the primary endpoint for VGX-3100X and Placebo, respectively. The primary hypothesis of superiority is:

$$H_0: \delta \leq 0 \textit{ vs. } H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [27]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

The secondary efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. It also includes subjects who underwent early intervention prior to this time frame; these subjects are considered as failures for the efficacy endpoints. Table 13 provides details for the definition of the primary endpoint response.

Table 13. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 or HPV-18 at Week 36 AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

Exploratory analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) colposcopy results, c) cytology results, and d) HPV results. As each of these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

Other exploratory analyses will examine durability of clearance of HPV-16 and/or 18 infection from cervical tissue at Weeks 62 and 88, and clearance of HPV-16 and/or 18 infection from non-cervical tissue.

Descriptive statistics will be utilized; percentages of subjects who cleared will be presented by time point or anatomic location and treatment group.

8.10 IMMUNOGENICITY ANALYSES

Post-baseline cellular and humoral response magnitude may be compared between treatment groups using a difference in medians and associated non-parametric 95% CI. Post-baseline tissue response magnitude will be compared between treatment groups using a difference in means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [27]. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

Any AEs with a missing or partial onset date will be included in the overall AEs, but not be included within specified day-range summaries. AE duration will be calculated as (Stop Date – Start Date) + 1.

8.11.2 LABORATORY DATA

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

8.12 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

8.13 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the mITT population.

8.14 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes among subjects who receive VGX-3100X will be compared between those with excision versus those without excision, based on PRO endpoints. This comparison will utilize the median difference in endpoints or the difference in proportions of subjects with endpoints and associated non-parametric or Miettinen and Nurminen [27] 95% CIs, for continuous responses and binary responses, respectively.

8.15 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

A subject's regression outcome is missing if her CIN grade and HPV clearance at Week 36 cannot be determined. Any subject who had suspected disease progression before Week 36 will be considered a non-regressor regardless of the Week 36 result, even if missing.

8.16 INTERIM ANALYSIS

No formal interim analyses will be performed for this study. For reasons of futility (early evidence of poor efficacy of VGX-3100X) or safety issues, the DSMB could recommend stopping enrollment at any time. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

9 DATA COLLECTION, MONITORING AND REPORTING

9.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

9.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. This retention period may be superseded by applicable regulatory requirements (e.g. minimum of 25 years for Health Canada). The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.4 SAFETY AND QUALITY MONITORING

9.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100X group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The

DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses.
The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

9.4.2 PATHOLOGY ADJUCATION COMMITTEE

All cervical biopsies will be read by a central expert Pathology Adjudication Committee (PAC) to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of three pathologists. Each specimen will be read by two pathologists independently in a blinded fashion. If the two pathologists agree the reading will be considered the clinical disease status for the subject. If the readings of the first two pathologists are discordant, the third pathologist will review and if there is agreement among any of the three readings, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached. A fourth pathologist will be identified to support the PAC in the event that one of the other pathologists is absent.

9.4.3 CLINICAL MONITORING

Clinical Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
    - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
    - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Assure that the study facilities continue to be acceptable
    - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

9.5 ADVERSE EXPERIENCE (AE) REPORTING

To assure the safety of the subjects, information about all AEs (see Section 7.1), whether volunteered by the subject, discovered by investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

9.5.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the AE CRF. Safety events will be analyzed and summarized throughout the study. Emphasis will be placed on the following:

- Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately
- Unsolicited AEs, SAEs or UADEs will be collected and summarized for the entire study period

9.5.2 STUDY REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol. An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.3 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.4 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy. At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION:

EMAIL: Safety@inovio.com
SAFETY FAX: [redacted] or [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms and any supporting documents to the Sponsor is as an attachment to an e-mail message, to the email addresses as indicated above and by facsimile (Fax), to include a fax coversheet that identifies the reporter and contact information to the designee.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Event
- Study number
- Subject number (SID) and initials
- Investigational Device serial number
- Lot numbers
- Reporter name and contact information

In the case of a "minimum report" (one that is solely comprised of the information bulleted above), a more detailed follow-up report will be sent as soon as more information becomes available but no later than 5 calendar days after the date of the initial report. The investigator will supply the Sponsor and the IRB with any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

9.5.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation.. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.3 and 7.1.4).

9.5.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint is defined as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution." All product complaints that meet this definition must be reported to the sponsor with 10 days of discovery

A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled.

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The

error reporting form must be completed and emailed to the Sponsor at [redacted] as shown in Appendix B.

9.6 STUDY DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

10 ETHICS

10.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2 INSTITUTIONAL REVIEW BOARD OR INSTITUTIONAL ETHICS COMMITTEE (IRB/IEC)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/IEC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/IEC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/IEC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

10.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

11 PROTECTION OF HUMAN SUBJECTS

11.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

11.2 COMPLIANCE WITH IRB/IEC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator must be provided to Sponsor.

11.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

11.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

11.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Device used in this study however will be asked to complete a subject diary card during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

11.6 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the sponsor in all participating countries and is fully supporting the study. Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted.

13 PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

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15 APPENDICES

15.1 APPENDIX A: SUBJECT DIARY CARD

Subject Diary

HPV-301

Subject #: _____

Injection Date:_____

Note to Participant:

For questions or problems, please contact your Site Coordinator.

Name: _____

Telephone: (_____) _____

Email (optional): _____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

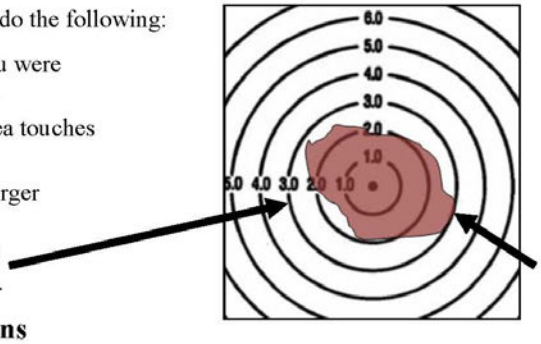
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 0: Evening of Injection Subject #: _____ Date: _____/_____/_____

Sometime during the evening on the day you were injected, fill out the information below. The items on this page refer to the time from your injection to 11:59 p.m. on the day of injection (Day 0). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst the symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 2.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

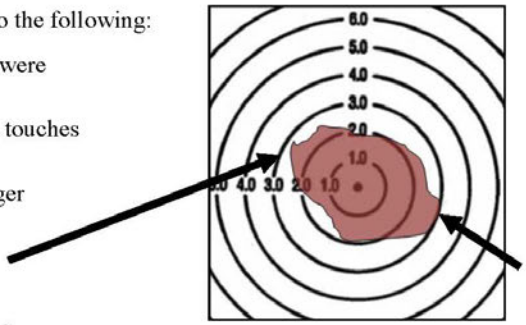
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 1: 1 Day After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 1). If any of the information changes after you fill out this page but before 11:59 p.m. tonight make any necessary changes below.

Temperature

Evening Temp.: _____ ºC or ºF (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 4.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

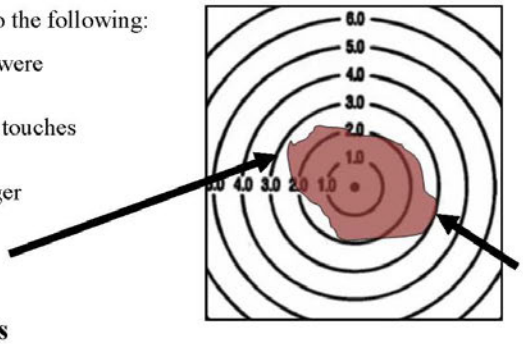
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 2: 2 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 2). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ ºC or ºF (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describesyour worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 6.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

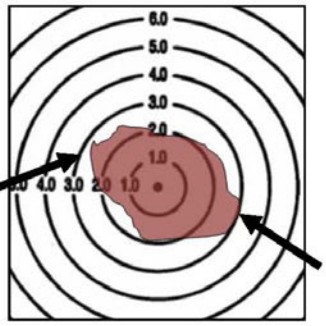
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 3: 3 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 3). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ ºC or ºF (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m.tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 8.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

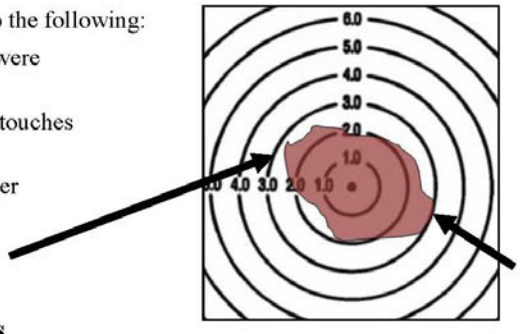
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 4: 4 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 4). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ ºC or ºF (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 10.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

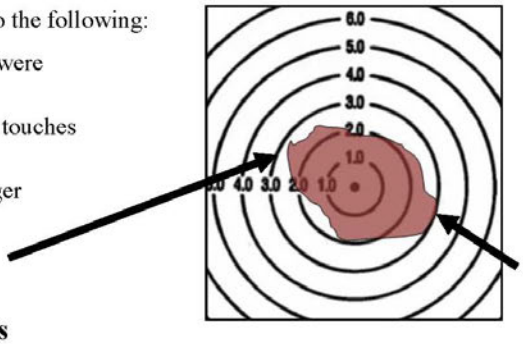
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 5: 5 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 5). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ ºC or ºF (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 12.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

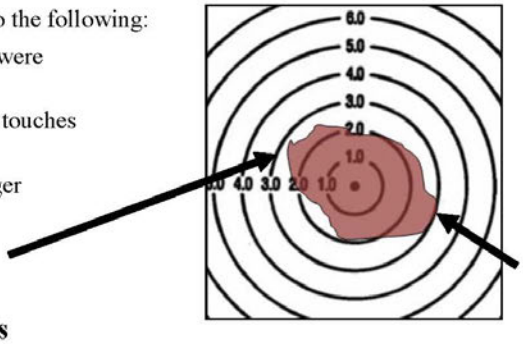
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 6: 6 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 6). If any of the symptoms you reported on previous pages have not gone away ("resolved"), you will need to let the Site Coordinator or Doctor know.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 14.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

15.2 APPENDIX B: ERROR REPORTING FORM

inovio PHARMACEUTICALS

CELLECTRA® 5PSP Device Error Form

Please complete the form and fax to (267) 440-4242 or scan the form to [redacted]

Protocol#_____ **Site#** _____ **Subject ID** _____ **Week#**_____ **Visit Date**_____

DEVICE INFORMATION

CELLECTRA® 5PSP Base Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the front cover

CELLECTRA® 5PSP Handset Serial No ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the handle

CELLECTRA® 5PSP Array Lot No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the package

Time of Treatment: _____

Type and Location of Treatment: ☐ **IM** ☐ **ID**
☐ **R**ight Arm ☐ **L**eft Arm
☐ **L**eft Quadriceps ☐ **R**ight Quadriceps
☐ Other Location, specify:_____

IM-5P ONLY, was the EP Guide used? ☐ YES ☐ NO

If EP Guide was used, please provide reason and include subject's BMI.

Was injection successful? ☐ YES ☐ NO

If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read EP successful? ☐ YES ☐ NO

If NO, please check all complications that led to failure and describe complication below

☐ Impedance Test Error message displayed, fill out Impedance Test Error section below
☐ Electroporation Error message displayed, fill out Electroporation Error section below
☐ EP aborted by trigger or keypad error message displayed
☐ Battery level too low for electroporation message displayed
☐ Difficulty inserting array into muscle or skin
☐ Other, please specify below

Describe device complication below (continue on back if necessary):

Total # of arrays used: _____ **Total # of attempts:** _____

Impedance Test Error (IM-5P Only)

Was the array fully inserted in subject's arm? (or thigh as applicable) ☐ YES ☐ NO
Were all attempts performed on the same day? ☐ YES ☐ NO
Was a different location used for each attempt? ☐ YES ☐ NO
Was a new array used for each attempt? ☐ YES ☐ NO

Please provide any additional information below (continue on back if necessary):

Electroporation Error

Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many_____
Was the array fully inserted in the subject's arm? ☐ YES ☐ NO
Was the array inserted perpendicular to the subject's skin? ☐ YES ☐ NO
Did the needles of the array appear damaged in any way? ☐ YES ☐ NO

If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.

Please provide any additional information below (continue on back if necessary):

15.3 APPENDIX C: GUIDELINES FOR COLPOSCOPY, BIOPSY, AND SURGICAL EXCISION

Colposcopy Procedure

It is recommended that all study colposcopies performed after informed consent be according the procedures recommended by the American Society of Colposcopy and Cervical Pathology (ASCCP):

1. Use warm, clean water to lubricate the vaginal speculum. Avoid other lubricant substances which could obscure results.
2. If the vaginal walls are lax, a lateral vaginal sidewall retractor aligned perpendicular to the speculum may facilitate visualization.
3. Examine the cervico-vaginal secretions and remove any excess mucus from the cervix with saline-soaked cotton swabs.
4. Obtain any required specimens required for cytology and HPV testing.
5. Using low-power magnification (5x to 10 x) inspect the cervix for obvious areas of abnormalities.
6. Swab or spray the cervix with 3-5% acetic acid. Reapply every 2-3 minutes during the examination.
7. Use the green or blue filter to examine blood vessels. Increase magnification (15x)
8. Identify the distal and proximal boarders of the transformation zone.
    a. The inner border is the entire 360-degree circumference of the squamocolumnar junction
        i. If the junction is proximal to the external os, in the canal, use a cotton-tipped applicator to pry either the anterior lip up or the posterior lip down or use an endocervical speculum
        ii. If the junction is not visualized in its entire circumference, the colposcopy is deemed inadequate
    b. The distal limit of the transformation zone may be identified by finding the most distal crypt openings or nabothian follicles in the lips of the cervix and drawing an imaginary line connecting these landmarks
9. Inspect the entire new squamocolumnar junction and detect and evaluate any abnormal areas.
10. Evaluate the upper third portion of the vagina.
11. Lugol or Schiller's solution may be applied to further define previously identified lesions.

Cervical Biopsies

Endocervical Curettage

ECC is to be performed using a kervorkian curette or equivalent instrument. Rotate and scrape the curette 360° in the endocervical canal and use a cytobrush to remove the specimen. Deposit the specimen onto a Telfa pad before depositing in the specimen vial containing 10% neutral buffered formalin solution and labeled with the subject identification (SID) number.

Ectocervical Biopsies

Ectocervical biopsies should only be performed prior to Week 36 if disease progression is suspected. Only the suspect lesion should be biopsied in that circumstance.

If the subject is eligible for 4 quadrant biopsy at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the subject's ID number and the quadrant number according to the figure below.
2. Perform and record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer

3. Perform colposcopic directed biopsies from all quadrants with lesions.
4. Multiple biopsies can be obtained of a lesion at the discretion of the investigator but must be uniquely labeled
5. If a quadrant is free of lesions, obtain a random biopsy at the squamocolumnar junction in that quadrant at 2, 4, 8, or 10 o'clock.
6. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Figure 1 – Biopsy Quadrant Numbers

Surgical Excision

For subjects undergoing surgical excision at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the SID number and the specimen type.
2. Record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform the LEEP or CKC per usual practice.
4. Specimen should be marked at 12 o'clock with suture or gentian violet ink for purposes of orientation
5. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

15.4 APPENDIX D: EQ-5D-5L HEALTH QUESTIONNAIRE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

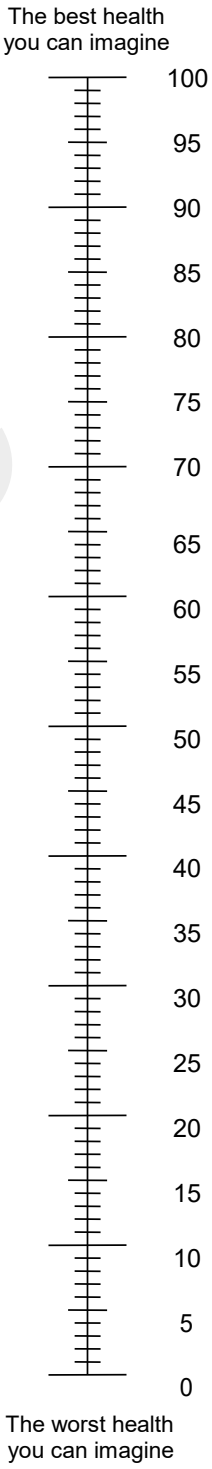
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.5 APPENDIX E: SF-36 V2 QUESTIONNAIRE

inovio

HPV-301 PROTOCOL

A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100X 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

Version 2.0

03 June 2016

Written by:

[redacted]

Date (DD-MMM-YYYY)

Reviewed and Approved by:

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

Biostatistician/ [redacted]

[redacted]

Date (DD-MMM-YYYY)

Medical Monitor

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

inovio

HPV-301 PROTOCOL

A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100X 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

Version 2.0

03 June 2016

Written by:

[redacted]

[redacted]
Date (DD-MMM-YYYY)

Reviewed and Approved by:

[redacted]

[redacted]
Date (DD-MMM-YYYY)

[redacted]

[redacted]
Date (DD-MMM-YYYY)

Biostatistician/ [redacted]

[redacted]

[redacted]
Date (DD-MMM-YYYY)

Medical Monitor

[redacted]

[redacted]
Date (DD-MMM-YYYY)

[redacted]

[redacted]
Date (DD-MMM-YYYY)

[redacted]

[redacted]
Date (DD-MMM-YYYY)

HPV-301

REVEAL I Trial

(Randomized Evaluation of VGX-3100X and Electroporation for the Treatment of Cervical HSIL)

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100X 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

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 2.1

10 June 2016

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100X 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

Short Title: REVEAL I Trial (Randomized Evaluation of VGX-3100X and Electroporation for the treatment of Cervical HSIL)

Biological Product: VGX-3100X

Protocol Number: HPV-301

Sponsor: Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462

Principal Investigator: [redacted], M.D., M.S.
[redacted]
Rutgers New Jersey Medical School
185 S. Orange Ave., MSB E-506
Newark, NJ 07103

Medical Monitor: [redacted], M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc.

CONFIDENTIAL

SUMMARY OF CHANGES

The following is a list of significant protocol changes from HPV-301 protocol version 1.0 dated 26 Apr 2016 to HPV-301 protocol version 2.0 dated 06 June 2016. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol.

1. Added rationale for selection of non-frozen formulation for phase 3 study
2. Added additional background information to Section 2 Study Design
3. Clarified inclusion and exclusion criteria
4. Administrative changes made throughout the protocol for clarification

Additional administrative and formatting changes were made to protocol version 2.0 dated 06June2016 resulting in protocol version 2.1 dated 10June 2016.

PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Investigator below constitute his/her approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, ICH-GCP guidelines, local legal and regulatory requirements as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____

Investigator – Signature Date (DD/MMM/YYYY)

_____

Investigator – Printed Name

Site Number: _____

Site Name: _____

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I LIST OF ABBREVIATIONS

AE	Adverse Event
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation with CELLECTRA™ 5PSP
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen

HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LSIL	Low Grade Squamous Intraepithelial Lesion
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

II CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100X 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)[1] of the Cervix	
Estimated Number of Study Centers and Countries/Regions: Approximately 100 Sites in up to 25 Countries	
Study Phase: 3	
Primary Hypothesis: Three 6 mg doses of VGX-3100X (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL[Cervical Intraepithelial Neoplasia (CIN)2, CIN3] of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit	
Study Drug Dose	6 mg (1 ml)
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device
Schedule	Day 0, Week 4, and Week 12 study visits
No. of Subjects	Approximately 165 subjects will be randomized in a 2:1 ratio to receive VGX-3100X or placebo
Study Duration	88 weeks
Primary Objective	Determine the efficacy of VGX-3100X compared with placebo with respect to **combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18**
Primary Endpoint	Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsy or excisional treatment) and **no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples** by type specific HPV testing at Week 36 visit

[1] Terminology based on 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP)

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100X delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of serious adverse events (SAE) and Unanticipated [Serious] Adverse Device Effects (UADE) for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2. Determine the efficacy of VGX-3100X compared with placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3. Determine the efficacy of VGX-3100X compared with placebo as measured by **virologic clearance of HPV-16 and/or HPV-18**	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples** by type specific HPV testing at Week 36 visit
4. Determine the efficacy of VGX-3100X compared with placebo as measured by **complete histopathologic regression of cervical HSIL to normal**	4. Proportion of subjects with **no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5. Determine the efficacy of VGX-3100X compared with placebo as measured by both **complete histopathologic regression of cervical HSIL to normal and virologic clearance** of HPV-16 and/or HPV-18	5. Proportion of subjects with **no evidence of LSIL or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) **and no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Week 36 visit
6. Determine the efficacy of VGX-3100X compared with placebo as measured by **histopathologic non-progression**	6. Proportion of subjects with **no progression of cervical HSIL** from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7. Determine the humoral and cellular immune response following administration of VGX-3100X compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 7b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 7c. Flow Cytometry response magnitudes at baseline and Week 15 visits

Exploratory Objectives	Associated Exploratory Endpoints
1. Evaluate tissue immune responses to VGX-3100X in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe the clearance of HPV-16 and/or HPV-18 infection from anatomic locations outside the cervix	2. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from outside the cervix (inclusive of oropharynx, vagina and peri-anus) at Week 36 Visit
3. Evaluate effect of HLA type on efficacy	3. HLA (per-locus and per-allele basis) in conjunction with **histologic regression of cervical HSIL** at Week 36 visit
4. Describe association of previous colposcopy, cytology and HPV testing results with histologic regression at Week 36	4. Colposcopy, cytology, and HPV test results at Weeks 15 and 28 visits in conjunction with histologic regression of cervical HSIL at Week 36 visit
5. Describe the durability of **virologic clearance of HPV-16 and/or HPV-18** for subjects treated with VGX-3100X compared with those treated with placebo	5. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Weeks 62 and 88 visits
6. Describe the patient-reported outcomes for subjects treated with VGX-3100X	6. The following two questionnaires: Short Form Health Survey, version 2 (SF-36v2™) and EQ-5D-5L™ will be self-administered prior to first dose (i.e. Day 0), following each dose, and at Weeks 28, 40 and 88 to measure score(s).

Study Design:

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled Phase 3 study to determine the efficacy, safety, and tolerability of VGX-3100X administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16 and/or HPV-18 (HPV-16/18). The composite primary endpoint is histologic regression of cervical HSIL, and clearance of the underlying HPV-16/18 infection. A sample of approximately 165 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100X or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization.

To be eligible for the study, women age 18 years and above must consent to participate and have biopsy/biopsies of the cervical lesion(s) at the time of screening. The biopsy slides are sent to a Pathology Adjudication Committee (PAC) in a blinded manner to establish the presence of cervical HSIL (CIN2, CIN3) prior to enrollment. Subjects must also have a cervical specimen test positive for HPV-16/18 by Cobas™ HPV test to be eligible for participation in the study.

All eligible subjects will receive three doses of VGX-3100X or placebo administered IM followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment is administered on Day 0, the second at Week 4, and the third (final) study treatment is administered at Week 12. The first dose is administered as soon as possible following confirmation of the cervical HSIL diagnosis and cervical sample positive for HPV-16/18 but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening.

Subjects are randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category ($\leq$25 vs. >25 kg/m^2), and (c) age category (<25 years vs. $\geq$25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The long term follow up plan following the Week 36 efficacy assessment will include safety, cytology and HPV testing for a period of approximately 1 year (Week 88).

Efficacy: Visualization of a normal appearing cervix by colposcopy and cytology are insufficient evidence to confirm disease regression. Therefore, disease regression will be based on histopathological assessment, which is considered the definitive method for diagnosis. Subjects will also be assessed by colposcopy, cytology, HPV testing at screening, Day 0, and Weeks 15, 28, 36, 62 and 88. Digital photographs of the cervix will be also used to document colposcopic exam findings.

Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (i.e. loop electrosurgical excision procedure (LEEP), large loop excision of transformation zone (LLETZ), cold knife conization (CKC)) or by biopsy (4 Quadrant Biopsy or 4 Quadrant Biopsy with Endocervical Curettage (ECC)) based upon the assessment at Week 28 of cytology, High Risk (HR) HPV status, and colposcopic findings (see Tables 4 and 5, for Minimally Required Procedures).

Safety: All subjects will be followed for 88 weeks.

Subjects will be monitored for:

1) Local and systemic events for 7 days following each investigational treatment as noted on a Participant Diary Card (PDC);
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

Data Safety & Monitoring Board (DSMB): The DSMB will meet quarterly to review unblinded safety data and histopathologic regression results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with histopathologic regression in the VGX-3100X group is unacceptably low compared to the placebo group. No formal interim analysis will be performed.

Immunogenicity: Humoral and cell mediated immune responses in response to VGX-3100X treatment may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

Virology: Cervical cytology samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 28, 36, 62, and 88 by Cobas™ HPV test. Additionally, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected to test for the presence of HPV-16/18. Vaginal, oropharyngeal and peri-anal samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 36, and 88.

HLA typing: The relationship between subject HLA types and efficacy responses will be explored using available PBMC sample collected for immunogenicity analysis.

Study Population

Inclusion Criteria:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Has satisfactory colposcopy, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Must have a cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Must have a cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL

b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
c) Women of Child Bearing Potential (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
    - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
    - Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
    - Intrauterine device or intrauterine system
    - Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject

11. Has normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

Exclusion Criteria:

1. Has microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose(i.e. Day 0);
3. Has cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
4. Has history of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
5. Has treatment for cervical HSIL or genital warts within 4 weeks prior to screening;
6. Is pregnant, breastfeeding or considering becoming pregnant during the study;
7. Has history of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
8. Has presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the investigator;
9. Has immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)

e) History of solid organ or bone marrow transplantation
f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results;

10. Has received any non-study, non-live vaccine within 2 weeks of Day 0;
11. Has received any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
12. Has current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
13. Has malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
14. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
15. Has history of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
16. Has sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
17. Has resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
18. Has prior major surgery within 4 weeks of Day 0;
19. Has participated in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
20. Has less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
21. Has tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
22. Has cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
23. Has metal implants or implantable medical device within the electroporation area;
24. Has active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
25. Is a prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
26. Is an active military service personnel;
27. Is a study-related staff or family member of study-related staff;
28. Has any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Table 1. Schedule of Events

Tests	Screening (-10 wks to -1 Day)	Weeks											
		Day 0	**8-14 days post Day 0 Phone Call**	**4 (± 4 days)**	**8-14 days post Wk 4 Phone Call**	**12 (± 4 days)**	**8-14 days post Wk 12 Phone Call**	**15 (± 1 week)**	**28 (± 1 week)**	**36 (± 1 week)**	**40 (± 2 weeks) Phone call**	**62 (± 2 weeks)**	**88 (± 2 weeks)**
Informed consent	X												
Medical History	X												
Demographics	X												
Socio-behavioral[a]	X									X			X
Inclusion / Exclusion	X	X											
Randomization		X											
Physical examination[b]	X	X		X		X		X	X	X		X	X
Vital signs	X[c]	X		X		X		X	X	X		X	X
Screening safety[d]	X												
Pregnancy Test[e]	X	X		X		X		X	X	X		X	X
HIV Testing by ELISA	X												
Blood immunologic samples[f]	X	X						X[g]		X			X
ThinPrep™ [h,i]	X	X						X	X	X		X	X
Cervical Digene swabs[i,j]	X	X						X	X	X			X
Colposcopy, lesion photography[k]	X[l]	X						X	X	X		X	X
Ectocervical biopsy[m]	X									X[n]			
Surgical excision[m]										X[n]			
OP[o], vaginal, anal swabs		X						X		X			X
Inject VGX-3100X/Placebo		X		X		X							
Post treatment assessment		X	X	X	X	X	X[p]						
Distribute PDC		X		X		X							
Review PDC			X		X		X[p]						
PROs		X	X		X		X[p]		X[q]		X [q]		X

[a] Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

[b] Full physical examination (PE) mandatory at screening and study discharge (Wk 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

[c] Screening vital signs must include a measured height and weight and calculated BMI;

[d] Screening 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 30 days prior to dose administration on Day 0;

[e] Negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

[f] At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum per time point (a total of at least 68 mL of whole blood and 8 ml serum should be collected prior to dosing on Day 0). HLA testing will performed once from an existing PBMC sample;

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

[i] Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

[j] Collected prior to the ThinPrep™ sample;

[k] Photographs of the cervix and the associated lesion must be collected prior to and after biopsies and at all colposcopic examinations;

[l] Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy and corresponding lesion photography is available;

[m] Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (i.e. LEEP, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 5 and 6);

[n] Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from entry and/or Week 36 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing;

[o] Oropharynx (OP) by oral rinse;

[p] Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

[q] PROs to be completed by subject 8-14 days after Week 28 visit and Week 40 phone call

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 HPV INFECTION, CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a HR HPV type [2, 3]. Up to 13000 women in the US alone are diagnosed with cervical cancer each year, which leads to an estimated 4120 deaths [4]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two genotypes are estimated to cause about 70% of all cervical cancers [5, 6].

Incident infection by HPV is characterized by ongoing viral replication and shedding and is associated with early histologic changes (grade 1 cervical intraepithelial neoplasia) when the female cervix is infected with HPV. Most cases of genital HPV infection clear spontaneously, but persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions of the cervix, HSIL which is inclusive of grade 2 and 3 cervical intraepithelial neoplasia (CIN2/3) [7]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [8, 9]. The basis for these changes are attributed to the viral proteins E6 and E7. Infected cells produce E6 and E7 constitutively which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia.

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade CIN caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [10]. This means that the large number of women who already have high grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they didn't respond to vaccination, must currently only rely upon surgery and the chance of spontaneous regression to treat their condition and avoid progression to cancer. Furthermore, the number of US-eligible teenagers who complete the prophylactic vaccination series remains low; 39.7% of US girls ages 13-17 completed their prophylactic HPV immunization series in 2014, which leaves a potentially vulnerable, under-protected population [11]. The current approaches to the management of cervical HSIL typically require surgery (i.e. LEEP/LEETZ, laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100X is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

1.1.2 VGX-3100X

VGX-3100X contains the identical plasmids to target HPV-16 E6/E7 and HPV-18 E6/E7 antigens that were included in VGX-3100. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100X and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18.

The initial formulation was designated as VGX-3100 (water-for-injection w/1% w/w poly-L-glutamate (WFI/LGS); frozen storage) and has been administered to more than 250 subjects in Phase 1 and Phase 2 clinical trials.VGX-3100X was developed to be a non-frozen formulation using saline sodium citrate (SSC) buffer. VGX-3100X was administered to 116 subjects in a Phase 1 clinical trial, HPV-101. In study HPV-101, three 6 mg doses of VGX-3100X, non-frozen formulation were delivered intramuscularly followed by electroporation with CELLECTRA™ 5P to healthy adults. Based upon interim analysis data at study Week 14, the non-frozen formulation was considered non-inferior to the frozen formulation based upon a 2-fold rise in overall Spot Forming Units (SPU) to the antigens encoded by the plasmids per 10^6 Peripheral Blood Mononuclear Cells (PBMC) as measured from baseline to Week 14 using the interferon-γ ELISpot assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or HPV-18. The Phase 2b study, HPV-003, enrolled 167 subjects with high grade cervical dysplasia from seven countries and one United States Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, United States and Puerto Rico). Subjects were randomized in a 3:1 ratio to the treatment arm (VGX-3100) or the placebo arm, respectively. All subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histopathology. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol and modified intent to treat analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.3 ELECTROPORATION

VGX-3100X is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity

[12, 13]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [14, 15]. This technology has been used for more than three decades by molecular biologists for cell transfection and has demonstrated versatility in use, as shown by its functionality in combination with a range of molecules, tissue types, disease indications, and across species [16].

The CELLECTRA™ device developed by Inovio is used for investigational purposes to administer plasmid-based DNA, in both prophylactic and therapeutic settings. Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency, and has demonstrated that the device helps to elicit favorable immunogenicity in several species (e.g., mice, pigs, and rhesus macaques) [17, 18].

VGX-3100 has been administered throughout Phase 1 and Phase 2 investigations with the CELLECTRA™ 2000 device. A next generation device, CELLECTRA™ 5PSP, will be used in Phase 3. Both designs of the CELLECTRA™ device enhance the intracellular uptake of VGX-3100X by the delivery of electrical current, and the electrical current delivery and pulse pattern (electroporation) is identical in both designs. CELLECTRA™ 2000 involves a manual injection of VGX-3100X while the CELLECTRA™ 5PSP device will automate the intramuscular delivery of VGX-3100X and delivery of the EP pulses triggered by a single button press. Neither the dosage nor volume of VGX-3100X administered differs between the two devices. Administration of VGX-3100X with the CELLECTRA™ 5PSP also allows selection of the needle array length from 13 to 19 to 25 mm depending on the estimate of the recipient's subcutaneous fat and muscle tissue.

The technology differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design (Table 2) are not significant and do not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, environmental specifications, and sterilization or performance specifications. The material changes are to the outer housing of the device and not to patient-contacting materials.

Table 2. Comparative Device Overview

	CELLECTRA™ 5PSP	CELLECTRA™ 2000
Array Specifications		
Electrode Number and Material (no bore)	5 Stainless steel, 304 electrodes pentagonal arrangement	5 Stainless steel, 304 electrodes pentagonal arrangement
Electrode Length	1.555 ± .020" (39.5mm)	1.555 ± .020" (39.5mm)
Electrode Gauge	22 Gauge (0.0278-0.0280 inch diameter)	21 Gauge (0.028±0.001 inch diameter)
Electrode Trocar Tip	15 ± 2°	15 ± 2°
Array Housing	Bayer Makrolon 2458C and Loctite 3921	GE Plastics (Sabic) Lexan HPS2
Sterilization Method and Sterility Assurance Level (SAL)	Gamma Irradiation- kGy To Be Determined SAL 10^{-6}	Gamma Irradiation 25-40kGy SAL 10^{-6}
VGX-3100X IM Injection Method	Automated (Handset mediated)	Manual (needle and syringe)
Injection Needle Material (full bore)	Stainless steel, 304	Stainless steel, 304
Injection Needle Length	2.102 ± .020" (54.4mm)	2.0" hypodermic needle recommended
Injection Needle Gauge	21 Gauge (.03250-0.03200 inch diameter)	21 Gauge
Injection Needle Trocar Tip	15° (double ended)	15° (single ended)
VGX-3100X IM Injection Depth	13, 19 and 25mm	13 and 19 mm
VGX-3100X IM Injection Volume	1.0±0.1mL	1.0±0.1mL
Electroporation Parameters		
Voltage	40-200 V maximum (varies with subject tissue impedance; 12V for device operation)	40-200 V maximum (varies with subject tissue impedance; 7.2V for device operation)
Pulse Width	52 milliseconds (ms)	52 milliseconds (ms)
Pulse Current	0.5 A; 1.0 A max	0.5 A ; 1.0 A max
Maximum Phase Charge	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses
Frequency	Up to 4 Hz between pulses	Up to 4 Hz between pulses

Benchtop design verification testing and a non-significant risk device functionality study will be completed prior to Phase 3 to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™ 5PSP device design meeting its safety and performance specifications, and no change to the administration of VGX-3100X by electroporation. Inovio's device experience demonstrates that delivery of electroporation pulses into muscle immediately following injection of DNA plasmids is well-tolerated in humans and no significant safety issues have been identified [19-21].

1.1.4 SELECTION OF STUDY DESIGN

This Phase 3 study employs a prospective, randomized, double-blind, placebo controlled study design to further demonstrate the safety and efficacy of VGX-3100X followed by EP in women with cervical HSIL associated with HPV-16/18. The primary clinical hypothesis is that VGX-3100X is a surgery-sparing, therapeutic option for the treatment of cervical HSIL and the underlying, pathogenic HPV-16/18 infection, which is supported by the findings of the Phase 2b trial. A placebo-controlled study is selected for this trial because it provides scientific rigor to distinguish an effective treatment, particularly in cervical HSIL for which spontaneous regression does occur.

1.2 DOSE AND REGIMEN RATIONALE

A total dose of 6 mg VGX-3100X DNA has been selected for this study based on previous human experience with both VGX-3100 and VGX-3100X, preclinical data with VGX-3100X and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 3) without significant safety issues [19].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a true effect rather than random variation. Adverse events from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in the Phase 2b study. The results obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Table 3. Percent of Protocol HPV-001 Subjects Responding and Average SFU/10^6 PBMC in Responders for each Antigen by Cohort in Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	**%Response**	**AVG**	**%Response**	**AVG**	**%Response**	**AVG**
HPV-16E6	33%	107	50%	243	50%	1341
HPV-16E7	17%	198	50%	104	67%	143
HPV-18E6	50%	359	50%	338	83%	664
HPV-18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

1.3 RISKS/BENEFIT ASSESSMENT

1.3.1 RISKS ASSOCIATED WITH CURRENT THERAPEUTIC OPTIONS

Currently, treatment of women with cervical HSIL usually consists of either surgical removal of the affected tissue by CKC, LEEP, ablative therapy via laser, or cryotherapy. All treatments for cervical HSIL are associated with a variety of short and long term general and reproductive health risks as listed in Table 4.

Table 4. Risks Associated with Surgical Treatments for Cervical HSIL

Surgical Treatments for Cervical HSIL	**Risks**
CKC LEEP Ablative therapy (Laser or Cryotherapy)	Pain
	Exposure to anesthesia
	Heavy bleeding
	Infection
	Menstruation problems
	Cervical stenosis (can lead to alteration of squamo-columnar junction)
	Shortening of the cervix
	Decreased fertility/difficulty getting pregnant
	Cervical incompetence
	Pre-term birth and related low birth weight
	Incomplete treatment of cervical dysplasia
	Inadequate treatment of an occult early invasive cancer

Adapted from *FAQs Loop Electrosurgical Excision Procedure (LEEP) American College of Obstetricians and Gynecologists (2014) [11]*.

More importantly, none of the currently available surgical treatments for cervical HSIL eradicate the underlying cause of the high grade cervical dysplasia, persistent infection with one or more of the high-risk HPV types, and therefore, leaves patients at risk for recurrent cervical HSIL as well as high grade dysplasia of the vulva and vagina due to the potentially broader infection of the genitourinary area.

Although professional guidelines typically advocate immediate excisional therapy for adults with cervical HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [8]. The risk of a "missed diagnosis" of an occult early invasive cervical cancer exists for all current treatment modalities including surgical and ablative therapies. Furthermore, approximately 17-18% of patients with high grade CIN will experience recurrence of dysplasia following surgical intervention [8], which illustrates that current standard of care for cervical dysplasia requires improvement. The study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult early invasive cervical cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent cervical colposcopy, cytology and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced gynecologists, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

1.3.2 POTENTIAL RISKS OF STUDY PARTICIPATION

A risk associated with VGX-3100X for the treatment of high grade cervical dysplasia are the injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild (e.g. erythema) and limited to a few days in duration at most.

A second risk is the "delay" in "definitive treatment" of the high grade cervical dysplasia and the "missed diagnosis" of an occult early invasive cervical cancer for the VGX-3100X non-responders or placebo recipients, who do not spontaneously regress. This risk is mitigated by careful serial cytology, HPV testing, and colposcopic exams, throughout the course of the study, and the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. Also, only investigators who are experienced in the management of cervical cancer will be chosen, and they will have the option of performing additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression.

A DSMB will also advise the Sponsor if it appears that the frequency of regression in the VGX-3100X group is unacceptably low compared to the placebo group. These measures should minimize the risk - even perhaps below that of standard care - of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. All subjects with suggestion of residual disease will undergo excisional therapy by CKC or LEEP at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Tables 4 & 5) to provide histopathologic confirmation of regression. In the Phase 2b study, the rate at which microinvasive cancer was found in larger

surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

1.3.3 POTENTIAL BENEFITS OF STUDY PARTICIPATION

All currently accepted treatments for high grade cervical dysplasia are surgical procedures (LEEP, CKC, Laser ablation) which are all associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding and/or infection, damage to other organs, shortening and/or deformation of the cervix, pain, etc. Due to the risk of shortening and/or deformation of the cervix there are additional well accepted risks including cervical stenosis, infertility, cervical incompetence, preterm birth, and inability to visualize the transformation zone. Additionally, none of the surgical treatments systemically address the underlying oncogenic root cause, the high risk HPV infection in the lower genital tract, which leaves an underlying risk for further disease manifestations and transmission of HPV. VGX-3100X+ EP is not associated with any of the risks associated with the surgical procedures outlined above (except for pain, which is transient, very quickly-resolving, and restricted to the deltoid/quadriceps treatment site) and has demonstrated the ability to not only eradicate the high grade dysplasia but also the ability to eradicate the underlying HPV infection. Subjects receiving placebo, who represent women of child-bearing potential, may benefit from the opportunity to be closely managed under careful surveillance over the course of this study and those who regress spontaneously will be able to avoid excisional therapy.

2 STUDY DESIGN

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled study to determine the efficacy, safety, and tolerability of VGX-3100X administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18.

A sample of approximately 165 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100X or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization.

Subjects will be randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category ($\leq$25 vs. >25 kg/m^2), and (c) age category (<25 years vs. $\geq$25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of

cervical HSIL. Subjects must also have a cervical specimen test positive for HPV-16/18 by Cobas™ HPV test to be eligible for participation in the study.

2.1 ENDPOINT ASSESSMENT

In the Phase 2b study, subjects were randomized 3:1 to the VGX-3100 arm or the Placebo arm. All subjects were scheduled to receive treatment on Day 0, Week 4 and Week 12 and undergo repeat cervical biopsy or surgical excision (i.e. LEEP, LLETZ, CKC) of the cervix at Week 36 to assess efficacy. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit, and the secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less.

The primary endpoint for the Phase 3 study is based upon the results of the Phase 2b study. Given that HPV persistence is an important factor in the clinical progression of dysplasia and also based upon the findings of the secondary objective of the Phase 2b study, the responder definition for the Phase 3 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16/18.

The proportion of subjects who achieved this endpoint in the Phase 2b study was 39.5% of VGX-3100 subjects versus 15.4% for placebo, in the modified-intention-to-treat analysis. The composite endpoint of histologic regression and virologic clearance will be primary in the Phase 3 study, and histologic regression endpoint will be a secondary endpoint.

2.1.1 HISTOLOGY ASSESSMENT

Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Digital photographs are also used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression will be is obtained at Week 36 either by excision (i.e. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or by 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings as outlined in Tables 5 and 6 for subjects 25 years and above and below 25 years, respectively.

Table 5. Minimally Required Procedure at Week 36 for Subjects Age 25 Years and Above

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
25 and above	NA	NA	HSIL, ASC-H, AGC, Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	positive	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	negative	4Q biopsy and ECC
	unsatisfactory	no lesion	NILM	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Table 6. Minimally Required Procedure at Week 36 for Subjects Under 25 Years

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
18-24	NA	NA	Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	HSIL, ASC-H, AGC	NA	Tissue Excision
	unsatisfactory	no lesion	NILM, ASC-US, LSIL	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US, HSIL, ASC-H, AGC[b]	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

[b] if cytology result is AGC "favor neoplasia", tissue excision is recommended

2.1.2 VIROLOGIC (HPV) ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 15, 28, 36, 62, and 88. Also, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for testing of HPV-16/18. Vaginal, oropharyngeal and peri-anal

samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 15, 36, and 88 to assess virologic response to treatment at sites other than the cervix.

2.1.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 7) for the primary endpoint takes into account both histopathologic regression of cervical HSIL and virologic (HPV-16 and/or HPV-18) clearance from cervical samples since HPV persistence is an important factor in the clinical progression of HSIL. The responder definition also excludes subjects whose cervix is biopsied at any time between their initial biopsy to determine eligibility and the Week 36 endpoint tissue collection. This exclusion is included to reduce the potential for artefactual increases in the treatment effect caused by removal of HSIL tissue and potentially HPV-16/-18 by unplanned interval biopsies. To qualify as a responder, the subject must have: 1) an acceptable histology specimen at Week 36, which is interpretable by the independent PAC, and 2) an acceptable HPV ThinPrep™ sample at Week 36, with an associated valid HPV-testing result. A responder is defined as a subject with: 1) no histologic evidence of cervical HSIL and 2) no evidence of HPV-16 or HPV-18 at the Week 36 evaluation. Also, to be considered a responder, the subject must not have had an unscheduled cervical tissue sample obtained between study entry and the Week 36 visit. Conversely, any subject with: 1) histologic evidence of cervical HSIL at the Week 36 evaluation, OR 2) evidence of HPV-16 or HPV-18 at the Week 36 visit, OR 3) a cervical tissue sample obtained between study entry and the Week 36 visit will be designated as a non-responder.

Table 7. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 or HPV-18 at Week 36 AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

2.1.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100X treatment may be evaluated in blood samples taken at baseline (both screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC). Whenever possible, these studies may be performed on tissue sections from the diagnostic screening biopsy (pre-dose) and from tissue obtained post-dose(s) (Week 36).

2.2 TREATMENT PLAN

The three dose regimen of VGX-3100 appeared to be safe and well tolerated in the Phase 2b study, therefore all eligible subjects who consent to participate in the Phase 3 study will receive the same three 6 mg doses of VGX-3100X or placebo administered in 1 mL IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third (final) study treatment will be administered at Week 12 which is consistent with the Phase 2b study. The first study treatment will be given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16/18 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-16/18.

2.3 SAFETY MONITORING PLAN

Although cervical HSIL is thought to require years to progress to cervical cancer, subjects in the Phase 2b study were followed closely throughout. HPV testing (Weeks 14 and 24), cytology (Week 14) and colposcopy (Week 24) were all mandatory during the observation period prior to obtaining tissue for determination of the primary histologic endpoint at Week 36. Investigators were also instructed to perform additional testing (including biopsy) if disease progression was suspected. These instances were infrequent as only 11 unscheduled biopsies were deemed necessary over the course of the Phase 2b study. In addition, the rate at which occult microinvasive cancer was discovered after 36 weeks was less frequent than what is reported in the literature [22]. Both observations would imply that the mandatory monitoring employed in the Phase 2b study was sufficient; however cervical disease will be monitored even more closely in this Phase 3 study. Colposcopy, cytology and HPV testing will be required at 8 to 14 week intervals throughout the observation period leading up to the primary endpoint 36 weeks after the first dose. Although less frequent monitoring may be adequate, the more frequent monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy.

Safety monitoring will include:

- Local and systemic events for 7 days following each treatment as noted on a Participant Diary Card (PDC).
- All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

In the Phase 2b study, the safety profile was carefully evaluated and treatment with VGX-3100 was well-tolerated based on observations through Week 88 in all subjects. The most common adverse events were administration-site reactions, which included pain, tenderness, erythema and swelling, and were generally mild and limited to a few days in duration. Only erythema showed a statistically

higher incidence in VGX-3100 (78%) vs. placebo (57%) in the 7- and 28-day periods after a dose. One additional AE, sinusitis, was also statistically significantly increased over the course of the entire study period but resolved without sequelae in the VGX-3100 arm compared to the Placebo arm (10% vs. 0%).

As outlined above, safety monitoring and visit frequency has been designed to take into account the potential risk of delay in the usual treatment of the high grade cervical dysplasia and also the potential for a missed diagnosis of an occult early invasive cervical cancer for the VGX-3100X non-responders or placebo recipients, who do not regress. Serial cytology, HPV testing, and colposcopic exams are applied throughout the course of the study with the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. All subjects with suggestion of residual disease will undergo excisional therapy by LEEP or CKC at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Table 5 and 6) to provide histopathologic confirmation of regression. The use of a 4 quadrant biopsy in Phase 3 is a change from the approach used in Phase 2b to optimize the evaluation of histopathologic regression taking into consideration the inherent limitations of colposcopy and tissue biopsy samples in the absence of visible lesions [23].

In the Phase 2b study, the cervical tissue sample was initially read by a local pathologist and/or central pathology laboratory for rapid local medical management. The definitive histopathologic assessment was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US. Seven reports included the terms '(adeno)squamous cell carcinoma' or the premalignant condition of 'adenocarcinoma in situ' (AIS) in the final Phase 2b study results which included all 88 weeks of follow up. Three of the cases were reported as AIS, (2 VGX-3100, 1 placebo), out of which two cases (1 VGX-3100, 1 placebo) were confirmed as AIS by the PAC. AIS is a pre-invasive glandular lesion which can be difficult to capture on standard of care screening with initial punch biopsy and is more commonly identified by full excision (e.g. LEEP, conization). There were four reports that included the term squamous cell carcinoma, of which two were confirmed by the PAC, both in the VGX-3100 group. The other two cases (1 VGX-3100, 1 placebo) were diagnosed as CIN3 by the PAC. The rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

Importantly, investigators in the Phase 3 study will be chosen only if they are experienced in the management of cervical cancer as was the case in the Phase 2b study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analysis as outlined in Table 6. These measures should minimize the risk of progression of cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. The frequency of close monitoring by experienced investigators should minimize the risk of cancer progression on the study what is expected with standard of care.

2.3.1 DATA SAFETY & MONITORING BOARD (DSMB)

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will be scheduled to meet quarterly. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with regression in the VGX-3100X group is unacceptably low compared to the placebo group. However, no formal interim analysis will be performed.

2.4 LONG TERM FOLLOW UP PLAN

In the Phase 2b study, all subjects were scheduled to be followed for 1 year after the histopathologic assessment for the primary endpoint (to study Week 88). The establishment of efficacy based on histopathologic evidence dictated the removal of tissue at week 36 by either punch biopsy (ies) or more extensive surgical resection (i.e. LEEP, CKC). Subjects with colposcopic evidence of residual disease were to undergo LEEP/CKC. A higher proportion of patients who received placebo had a LEEP performed than those who received VGX-3100 (Table 8).

Cytology and HPV-16/18 clearance from the cervix was to be assessed at study Weeks 62 and 88 to evaluate for recurrence of dysplasia and HPV infection after removal of tissue at Week 36. Overall, in the phase 2b study, the majority of subjects had improved cytology and had cleared their underlying HPV-16/18 cervical infection by the Week 62 and 88 visits. For Weeks 62 and 88, there were no clinically meaningful differences noted between the subjects who received an excisional treatment (e.g. LEEP, CKC) and those that showed histopathologic regression and therefore only underwent a biopsy, as shown in Table 8 which summarizes the HPV and cytology results following Week 36.

Table 8. HPV-003 HPV and Cytology Results at Weeks 36, 62 and 88, mITT Population

		VGX-3100		Placebo	
Week	Test[a]	LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	00% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89% (42/47)	89% (24/27)	00% (10/10)
88	Pap	96% (52/54)	91% (43/47)	85% (23/26)	00% (11/11)

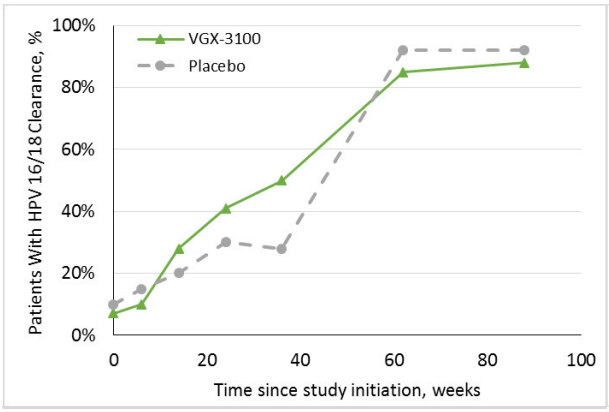
Abbreviations: NA, not applicable, Pap smear was not done at Week 36
[a] HPV = HPV-16/18 testing; Pap = cytology testing

[b] LEEP or CKC done, at or before the study week as specified
[c] Only biopsy done, at or before the study week as specified

Clearance of HPV-16/18 from the cervix was observed in both treatment groups (Figure 1a) at similar rates until after the second dose when clearance in the VGX-3100 recipients continued to rise while the rate appeared to plateau in the placebo group.

Figure 1. HPV-16/18 Clearance and Pap Smear Findings in Phase 2b mITT Population by Treatment Group

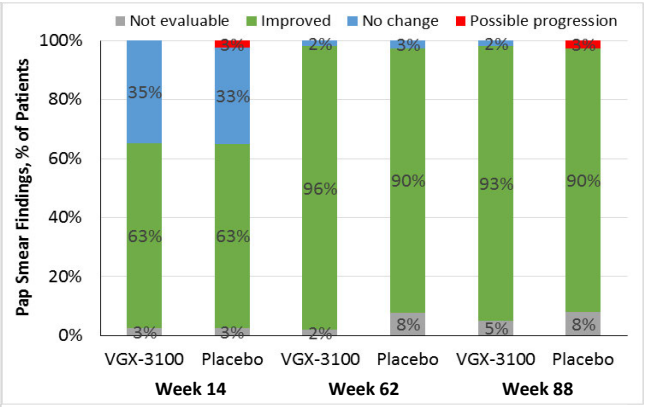
a.



No. of subjects

VGX-3100	123	62	118	116	115	108	103
Placebo	42	26	40	40	40	39	37

b.



No. of subjects

VGX-3100	118		108		103
Placebo	40		39		37

At Week 36, clearance was significantly higher among VGX-3100 subjects that had biopsy (63%) versus LEEP/CKC (41%), which likely reflects the association between clearance of the underlying HPV infection and the likelihood of having signs indicative of regression by colposcopic exam. HPV-16/18 clearance data (mITT population) post-Week 36 are described as follows: HPV-16/18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% (42/51) for VGX-3100 post Biopsy only, 96% (27/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post Biopsy only. HPV-16/18 clearance at Week 88 was 89% (48/54) for VGX-3100 post-LEEP/CKC, 89% (42/47) for VGX-3100 post Biopsy only, 89% (24/27) for Placebo post-LEEP/CKC, and 100% (10/10) for Placebo post Biopsy only.

The majority of subjects had cleared their underlying cervical HPV-16/18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups. Forty-seven of 53 (89%) and 46 of 49 (94%) subjects at Weeks 62 and 88, respectively (mITT population) with histopathologic evidence of CIN2/3 regression (regressors) in the VGX-3100 treatment group experienced HPV-16/18 clearance. Despite the use of therapeutic resection for many VGX-3100 recipients whose CIN2/3 did not regress by Week 36 (non-regressors), HPV-16/18 clearance rates were notably lower (85% at Week 88) compared to regressors.

In the subjects who initially cleared HPV-16/18 by Week 36, only one HPV-16/18 recurrence was identified at the Week 62 and 88 evaluations. Specifically, one subject who had HPV types 16 and 82 and CIN2 at screening, was HPV negative at Week 36, but tested HPV type 16 positive at Week

62, and then cleared HPV-16 at Week 88. The subject showed histopathologic regression at Week 36. No recurrences were identified in the eleven subjects in the placebo group with valid HPV data at Weeks 62 or 88. There were no (0/51) recurrences identified in the VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk as compared to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear cytology results at Week 62 were 93% (52/56) for VGX-3100 post-LEEP/CKC, 100% (51/51) for VGX-3100 post-Biopsy only, 93% (26/28) for Placebo post-LEEP/CKC, and 82%

(9/11) for Placebo post-Biopsy only. At Week 62, cytopathologic improvement was reported for 104 of 125 (83%) subjects in the VGX-3100 treatment group and 34 of 42 (83%) subjects in the placebo treatment group (mITT population).

There were no instances of possible progression, and all cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. Improvement compared to study entry for Pap smear cytology results at Week 88 were 96% (52/54) for VGX-3100 post-LEEP/CKC, 91% (43/47) for VGX-3100 post-Biopsy only, 85% (23/26) for Placebo post-LEEP/CKC, and 100% (11/11) for Placebo post-Biopsy only. At Week 88, possible progression (atypical glandular cells) was reported in a single Placebo subject in the post-LEEP/CKC group (3%) and no subjects treated with VGX-3100. All other cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. The majority of subjects showed improvement, and there was no meaningful difference between the Week 62 and Week 88 evaluations. These findings support that study subjects had no increased risk of progression based upon cytology as compared to standard of care.

The protocol-specified removal of dysplastic cervical tissue at Week 36 by either method substantially affected the clearance of HPV-16/18 and normalization of cytologic findings as expected, regardless of treatment group (Figure 1a, b). HPV-16/18 clearance rises at a sharp rate after tissue is removed at Week 36 whether the excision is wide (LEEP/CKC) or more limited (biopsy). Notably, the method of tissue collection at the Week 36 endpoint did not appreciably affect the HPV-16/18 clearance rates beyond Week 36 (Table 8). Based upon the Phase 2b results, the risk of progression or recurrence of cervical dysplasia is low and comparable to the rates observed post-LEEP/CKC in clinical practice. The long term follow up planned for this Phase 3 study will include safety, cytology and HPV-16/18 testing at 6 months and also 1 year following the Week 36 histopathologic assessment, which is highly conservative given the expectation that few subjects will have persistent evidence of disease after the removal of tissue at Week 36 which is supported by the findings in the Phase 2b study.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 HYPOTHESIS

Three 6 mg doses of VGX-3100X (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered IM followed by EP with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16/18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit.

3.2 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of VGX-3100X compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18	Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples by type specific HPV testing at Week 36 visit

3.3 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Endpoints
1. Evaluate the safety and tolerability of VGX-3100X delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit) 1b. Incidence and severity of serious adverse events (SAE) and Unanticipated [Serious] Adverse Device Effects (UADE) for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2. Determine the efficacy of VGX-3100X compared with placebo as measured by histopathologic regression of cervical HSIL	2. Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3. Determine the efficacy of VGX-3100X compared with placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in ThinPrep™ cervical samples by type specific HPV testing at Week 36 visit

Secondary Objectives	Associated Endpoints
4. Determine the efficacy of VGX-3100X compared with placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5. Determine the efficacy of VGX-3100X compared with placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6. Determine the efficacy of VGX-3100X compared with placebo as measured by histopathologic non-progression	6. Proportion of subjects with no progression of cervical HSIL from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7. Determine the humoral and cellular immune response following administration of VGX-3100X compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 7b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 7c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.4 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Endpoints
1. Evaluate tissue immune responses to VGX-3100X in cervical samples	Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe the clearance of HPV-16 and/or HPV-18 infection from anatomic locations outside the cervix	2. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from outside the cervix (inclusive of oropharynx, vagina and peri-anus) at Week 36 Visit

Exploratory Objectives	Associated Endpoints
3. Evaluate effect of HLA type on efficacy	3. HLA (per-locus and per-allele basis) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe association of previous colposcopy, cytology and HPV testing results with histologic regression at Week 36	4. Colposcopy, cytology, and HPV test results at Weeks 15 and 28 visits in conjunction with histologic regression of cervical HSIL at Week 36 visit
5. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100X compared with those treated with placebo	5. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
6. Describe the patient-reported outcomes for subjects treated with VGX-3100X	6. The following two questionnaires; Short Form Health Survey, version 2 (SF-36v2™) and EQ-5D-5L™ will be self-administered prior to first dose (i.e. Day 0), following each dose, and at Weeks 28, 40 and 88 to measure score(s).

4 SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36
7. Has satisfactory colposcopy, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;

8. Must have a cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Must have a cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) WOCBP is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
        - Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
        - Intrauterine device or intrauterine system
        - Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject
11. Has normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from enrollment in the study:

1. Has microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose(i.e. Day 0);
3. Has cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
4. Has history of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
5. Has treatment for cervical HSIL or genital warts within 4 weeks prior to screening;

6. Is pregnant, breastfeeding or considering becoming pregnant during the study;
7. Has history of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
8. Has presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the investigator;
9. Has immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
10. Has received any non-study, non-live vaccine within 2 weeks of Day 0;
11. Has received any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
12. Has current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
13. Has malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
14. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
15. Has history of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
16. Has sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
17. Has resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
18. Has prior major surgery within 4 weeks of Day 0;

19. Has participated in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
20. Has less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
21. Has tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
22. Has cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
23. Has metal implants or implantable medical device within the electroporation area;
24. Has active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
25. Is a prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
26. Is an active military service personnel;
27. Is a study-related staff or family member of study-related staff;
28. Has any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests Grade 3 toxicity attributable to the study treatment, the medical monitor and Investigator will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All randomized subjects should be encouraged to complete all study treatments and follow-up visits. A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule for follow-up and treatment of HSIL (CIN2, CIN3), and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the

rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/ WITHDRAWAL

The investigator or study coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1 – Safety Parameters.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the CRF:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death of subject
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the CRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a medical need to withdraw the subject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject from participation in the study
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.

- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including telephone calls, letter sent by certified mail or equivalent.
- Other: The subject was terminated for a reason other than those listed above, such as the termination of the study by the Sponsor

5 STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The active and placebo formulations to be used in this study are described in Table 9. Both IPs will presented in clear glass cartridges and will be injected intramuscularly.

VGX-3100X and placebo will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 9. Investigational Products

Product	Formulation	Dose
VGX-3100X	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Placebo	150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 BLINDING

This study is double-blinded with blinding maintained throughout the study by use of identical packaging for both the active product and the placebo. There is no difference in appearance for both the active product and the placebo.

The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is essential for proper clinical management of the subject, as judged by the investigator. It is preferred, but not required, that the investigator first contact the Medical Monitor to discuss options before unblinding the subject's treatment assignment. In case of non-emergency, investigator must contact Medical Monitor to discuss the options before unblinding the subject's treatment assignment.

The Sponsor's or designee's pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE, UADE, or AE of interest. No personnel directly involved with the study will be unblinded. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's treatment assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCT

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, double-panel label with tear-off. Both VGX-3100X and placebo labels will include, at minimum, the following information in Table 10:

Table 10. Example Labels for Investigational Product

Cartridges (primary container)	**Pouches** (secondary package)
VGX-3100X or Placebo Insert cap end IM administration Inovio Pharmaceuticals, Inc.	Study ID/Material ID VGX-3100X or Placebo Single-use, 1 mL Storage temperature, expiration date CAUTION: New Drug – Limited by United States Law to Investigation Use Inovio Pharmaceuticals, Inc.

5.4 HANDLING OF INVESTIGATIONAL PRODUCT

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Unless otherwise specified, IP will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Immediately upon arrival, IPs should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition.

Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

5.5 DISPENSING OF INVESTIGATIONAL PRODUCT

It is the responsibility of the Investigator to ensure that the IP is only dispensed to study subjects. It must be dispensed only from official study sites by authorized personnel according to local regulations.

When a subject is eligible for randomization, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration. The pouch must not be discarded until 1) administration is completed and 2) all pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator.

The device user manual and instructions for use will inform clinical personnel about placement of the IP cartridge into the device, as well as the steps for injection and electroporation.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused and/or partially used IP must be returned to Inovio Pharmaceuticals, Inc., or its designee, if not authorized by Inovio Pharmaceuticals, Inc. to be destroyed at the site.

The IP cartridge will be discarded along with the disposable array within a sharp's container at site.

All IP returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor.

If IP(s) are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor

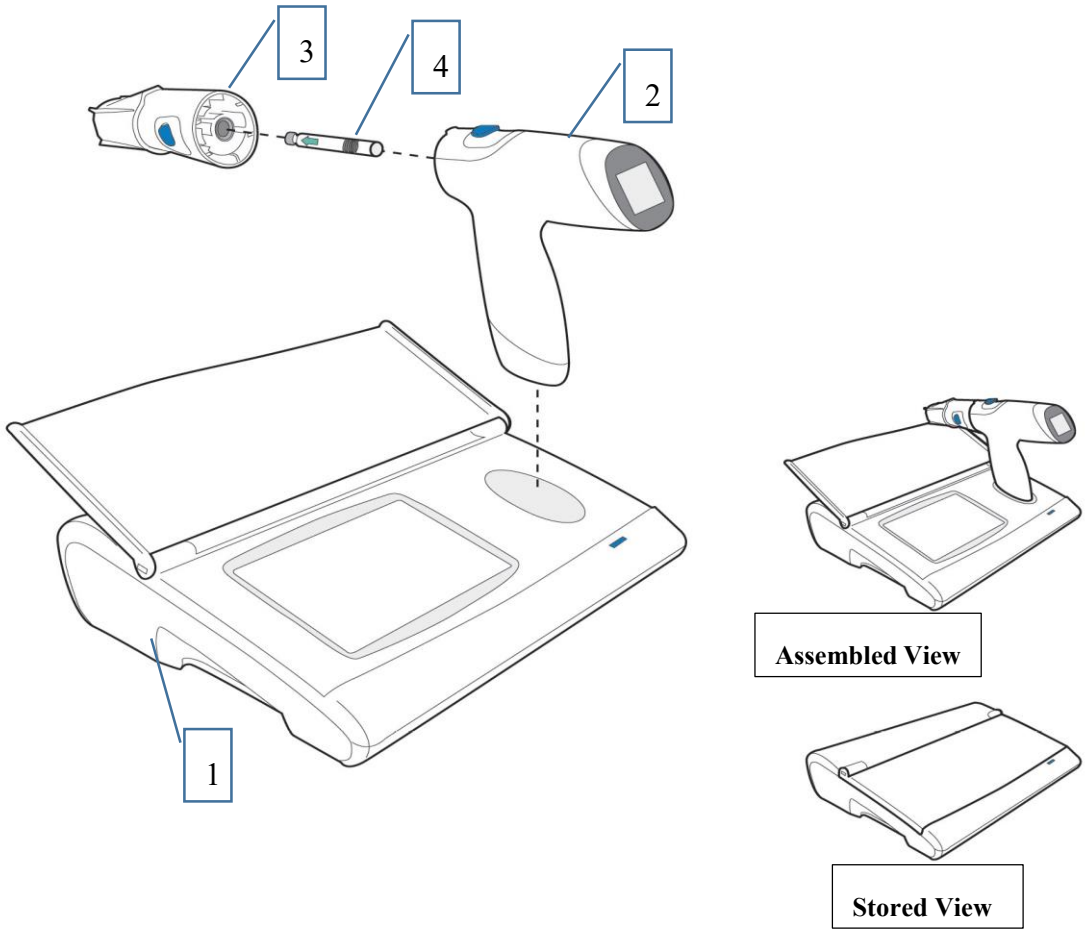
5.8 INVESTIGATIONAL DEVICE

The needle array component of CELLECTRA™ 5PSP device is provided sterile and is intended for single-use. CELLECTRA™ 5PSP device is intended to be used by qualified and trained healthcare professionals in clinical settings. The Investigator for this study will be trained in the use of the device.

CELLECTRA™ 5PSP has 3 main components that are used in conjunction with the drug cartridge (see Figure 2):

1. **Base** – Acts as a docking station for the Handset and as the primary display for entering subject information; must be used with the provided Power Supply
2. **Handset** – Controls delivery of the drug and electrical pulses
3. **Array** (single-use sterile) – Attaches to the Handset and contains the injection needle, electrodes and sensors used for drug delivery and electroporation.
4. **Drug Cartridge** (single-use) – a separate container-closure containing the IP solution. The Cartridge is inserted into the array for administration of the IP.

Figure 2. Components of the CELLECTRA™ 5PSP Device and Drug Cartridge



The CELLECTRA™ 5PSP device has unique features that make using it different from using other injection systems:

1. Each Handset is uniquely paired to a Base. The serial numbers on the bottom of the Base and Handset must match.
2. There is no communication between the Base and Handset when separated; the Handset must be placed onto the Base to share power or data.
3. The Handset has an internal battery that must be charged on the Base before use.
4. Needle depth is selectable on the Handset at the following lengths: 13 mm, 19 mm, or 25 mm. Even though the system provides a needle depth recommendation based on a Subject's height and weight, the user will be asked to manually enter the needle depth based on the protocol requirements (refer section 5.9), described
5. Injecting the placebo and delivering electrical pulses takes time (usually 10 seconds). The Handset will let you know when treatment is complete.
6. The Subject should be maintained in a safe and secure, braced position due to involuntary muscle spasms that may occur during delivery of the electrical pulses.

Before using the CELLECTRA™ 5PSP device, the Investigator and research staff must be trained by the Inovio Pharmaceuticals Inc. device trainer(s) and be requested to read the entire user manual and complete the Self-Assessment.

5.9 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the device are located in the CELLECTRA™ 5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training. Training will include review of the entire device user manual and instruction video and hands-on training. After training on the proper use of the CELLECTRA™ 5PSP device, intended users at each site will be required to demonstrate their competence in its use to Inovio or its designee.

Briefly, the Handset and Array should be prepared according to the instructions in the user manual. Remove the array from its packaging while avoiding contact with the end of the array that attaches to the handset, and insert the drug cartridge into the array with the arrow on the cartridge pointing away from the handset.

Attach the Array to the Handset and set the needle depth on the handset to the longest needle length judged to allow safe injection into the muscle per the investigator's assessment.

The subject must be in a safe and secure, braced position. The subject's body should touch the bed or be braced against the bed or have the study staff performing electroporation or assistant in ~~the~~ position to brace the subject's arm or leg (as appropriate) as the EP is administered. The user will then insert the CELLECTRA™ 5PSP needle array into the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) of the participant in accordance with the CELLECTRA™ 5PSP user's manual instructions. Once triggered by the user, the device will automatically deliver the blinded treatment followed by the EP pulses. The entire treatment period lasts for about 10 seconds.

The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel. Individuals whose credentials do not meet the relevant local requirements may perform the treatment procedure under both of the conditions below:

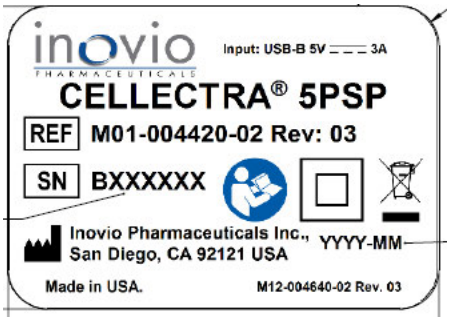
1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform the procedure.

Any deviation from the above procedures must be approved by the sponsor or its designee.

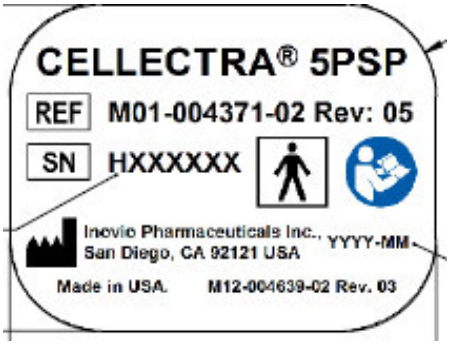
5.10 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

See below Figure 3 for example CELLECTRA™ 5PSP device component labels.

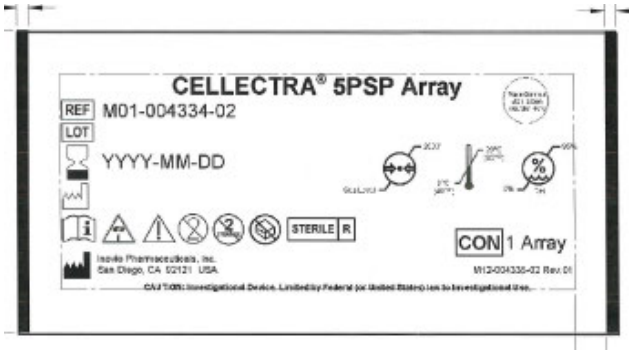
Figure 3. Device Labels (Base, Handset, Array)



BASE



HANDSET



ARRAY

5.11 HANDLING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual.

5.12 INVESTIGATIONAL DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining investigational device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational product. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP serial number, array lot number and the study drug lot number. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.13 RETURN OF INVESTIGATIONAL DEVICES

Upon completion or termination of the study, all investigational devices and unused components must be returned to Inovio Pharmaceuticals, Inc.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by the responsible Study Monitor.

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

After providing informed consent, subject's cervical biopsy tissue samples (e.g., formalin fixed tissue, paraffin-embedded tissue) and/or biopsy slides will be sent to the PAC for review by two study pathologists. Discordant results will be reviewed by a third pathologist to achieve a consensus diagnosis. Subjects must have a diagnosis of histologic HSIL (CIN2 or CIN3) confirmed by the PAC and a screening cervical specimen (i.e. ThinPrep™) test positive for HPV-16 and/or HPV-18 by Cobas™ HPV test to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

- Biopsy specimens and colposcopic photographs obtained within 10 weeks prior to Day 0 as part of standard of care before the informed consent may be used as part of the screening and evaluation process.
- If the pathology results of the initial biopsy obtained as part of standard of care are available confirming the presence of HSIL (CIN2 or CIN3), those biopsy slides or sample(s) may be sent directly to the PAC for concurrence after the subject has signed the informed consent.
- For those individuals diagnosed with cervical HSIL by a local pathologist, where the initial biopsy slides or tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, colposcopy with cervical photography may be performed and an additional biopsy sample may be collected during screening at the discretion of the investigator and consent of the subject. The additional biopsy sample may be sent directly to the PAC for review, if allowable per local or institutional guidelines.

The assessments during the screening period will determine the subjects' continued eligibility for the study and also their ability to comply with protocol requirements by completing all assessments.

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to 1 day prior to dosing on Day 0 – except for the safety laboratory collections/assessments, which must be performed within 30 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy with lesion photography and cervical biopsy
- Demographics; including age, and race/ethnicity
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Determination of eligibility per inclusion / exclusion criteria
- Full Physical Examination (including height, weight and BMI measurements)
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 30 days prior to Day 0);
- Urine pregnancy test
- Serology (HIV Antibody) (within 30 days prior to Day 0)
- Whole blood (at least 34 mL) and serum (at least 4 mL) for baseline immunologic assay
- 2 Digene cervical brush samples

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluation will be performed on **Day 0 prior to study treatment:**

- Determination of eligibility per inclusion / exclusion criteria
- Randomization
- Targeted Physical Exam
- Vital signs
- Urine pregnancy test
- Whole blood (at least 34 mL) and serum (at least 4 mL) for baseline immunologic assay (a total of at least 68 mL of whole blood and 8 ml serum should be collected prior to dosing on Day 0)
- Colposcopy with lesion photography
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) sample by oral rinse and vaginal and anal swabs
- Patient-Reported Outcomes (PROs) completion

Study treatment will be administered and the following evaluations will be performed on **Day 0 post-treatment:**

- Post treatment adverse event and injection site reaction assessment within a minimum of 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)

- Download EP data from device

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review Day 0 PDC
    - The subject should submit their PDC (via email, fax, mail) to site personnel prior to the phone visit. If the PDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the PDC should be collected and reviewed at the next in-person study visit. After completing a review of PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.3 WEEK 4

The following study evaluation will be performed on **Week 4 prior to study treatment (± 4 days):**

- Targeted Physical Exam
- Vital signs
- Urine pregnancy test
- Collect PDC for dose 1

The following study evaluations will be performed **on Week 4 post treatment:**

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 2
    - The subject should submit their PDC (via email, fax, mail) to site personnel prior to the phone visit. If the PDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the PDC should be collected and reviewed at the next in-person study visit. After completing a review of PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.5 WEEK 12

The following study evaluation will be performed on **Week 12 prior to study treatment (± 4 days):**

- Targeted Physical Exam
- Vital signs
- Urine pregnancy test
- Collect PDC regarding Dose 2

The following study evaluations will be performed **Week 12 post treatment**:

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device

6.2.6 8-14 DAYS POST DOSE 3 PHONE CALL

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 3
    - The subject should submit their PDC (via email, fax, mail) to site personnel prior to the phone visit. If the PDC is not received in advance, site personnel should review all diary elements verbally. The hard copy of the PDC should be collected and reviewed at the next in-person study visit. After completing a review of PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation.
- PRO completion

6.2.7 WEEK 15

The following study evaluations will be performed on **Week 15 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood (at least 51 mL) and serum (at least 4 mL) for immunologic assays
- Post-treatment injection site reaction assessment
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) by oral rinse and vaginal and anal swabs

- Collect PDC
- Colposcopy and lesion photography

6.2.8 WEEK 28

The following study evaluations/actions will be performed on **Week 28 ± 1 weeks:**

- Targeted physical Assessment
- Vital signs
- Urine pregnancy testing
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography to assess for possible disease progression
- PRO to be completed by subject 8-14 days after Week 28 visit

6.2.9 WEEK 36

The following study evaluations will be performed on **Week 36 ± 1 week:**

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Whole blood (at least 34 mL) and serum (at least 4 mL) for immunologic assays
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Oropharynx (OP) by oral rinse and vaginal and anal swabs
- Colposcopy and lesion photography
- Biopsy or surgical excision

The investigator will utilize information collected at Week 28 to determine the appropriate method for obtaining tissue for histopathologic assessment as described in Tables 4 & 5 for minimally required procedure (4 quadrant biopsies, 4 quadrant biopsies and ECC, or excision).

6.2.10 WEEK 40 PHONE CALL

The following study evaluations will be performed on **Week 40 ± 2 weeks** via a phone call:

- Review of histology results as read by PAC from Week 36
- PRO to be completed by subject 8-14 days after Week 40

6.2.11 WEEK 62

The following study evaluations will be performed on **Week 62 ± 2 weeks:**

- Targeted physical assessment
- Vital Signs
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography

6.2.12 WEEK 88

The following study evaluations will be performed on **Week 88 ± 2 weeks:**

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Full Physical Exam
- Vital Signs
- ThinPrep™ sample for HPV PCR and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical brush samples
- Colposcopy and lesion photography
- Whole blood (at least 34 mL) and serum (at least 4 mL) for immunologic assays
- Oropharynx (OP) by oral rinse and vaginal and anal swabs
- PRO completion

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with [redacted] (e.g., [redacted]). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.3 SAFETY EVALUATIONS

6.3.3.1 Physical Exam

A full physical examination (PE) will be conducted during screening and study discharge. It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

A targeted physical assessment will be performed at other visits as determined by the investigator or directed per subject complaints. The injection site is to be assessed by the study personnel at 30 minutes after each study treatment.

6.3.3.2 Vital Signs

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 Weight and Height

Weight (kg) and height (cm) will be collected at screening in order to calculate the BMI (BMI = kg/m^2).

6.3.3.4 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. The medical history will include a) any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s), and b) if treated previously for CIN, the respective treatment type(s) and date(s).

6.3.3.5 Socio-Behavioral Assessment

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained.

6.3.3.6 Laboratory Evaluations

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count w/ differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- SGPT (serum glutamic-pyruvic transaminase)/ALT
- BUN (blood urea nitrogen)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- CPK (creatine phosphokinase)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose ≥ 1+) a microscopic examination should be performed.

6.3.3.7 Demographics

Demographic information will be collected via self-report (unless noted otherwise), including the following:

- Age (via date of birth)
- Race/ethnicity

6.3.3.8 Urine Pregnancy Testing

For subjects of reproductive potential, a negative spot urine pregnancy test is required prior to each study treatment, colposcopy and surgical excision.

6.3.3.9 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QTcb or QTcf, ST segment, Twave as well as an investigator

assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as “clinically significant (CS)” or “not clinically significant (NCS)” by the investigator

6.3.3.10 Subject Post Treatment Assessments

PDC will capture subject reported local and systemic events for 7 days after the study treatment as shown in Appendix A.

The subject will be provided a PDC and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PDC will be reviewed with the subject and research staff at 8 -14 Days post-dose.

The study staff will review the PDC for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse event accordingly.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a 3-dose series of either 1 ml VGX-3100X or Placebo by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with the CELLECTRA™ 5PSP. Study treatment must not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.4.1 RISKS OF TREATMENT PROCEDURES

Table 11 summarizes reported AEs and potential risk to study treatment.

Table 11. Summary of Reported Adverse Events and Potential Risks or VGX-3100X Delivered IM EP with CELLECTRA™ 5PSP

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration
Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury • Disruption of function of implanted electronic medical devices (if CELLECTRA™ 5PSP device is not used per User Manual) • Exacerbation of unstable cardiac disease • Effects on the fetus and on pregnancy

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO TREATMENT

Subjects may be offered topical anesthetic (i.e. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be

allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening will be performed for inclusion into the study as listed in section 6.1.1.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and within minimum of 30 minutes after each study treatment and at 2 to 4 weeks post study treatment visits. They will also be advised to record local and systemic AEs for 7 days on a PDC as shown in Appendix A.

A Medical/Clinical Assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 12. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, previously-validated patient-reported outcomes (PRO) instruments will be provided to the subjects. PRO questionnaires will include the following, along with the license holder, respective numbers of items and domains, and listed domains:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily
- pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [24] (See Appendix D for sample questionnaire).
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status via VAS) [25, 26] (see Appendix E for sample questionnaire).

The PRO instruments will be provided to subject and will be instructed to complete the questionnaire at the following time points:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- 8-14 days post dose 2
- 8-14 days post dose 3
- 8 -14 days post Week 28
- 8-14 days post Week 40
- Week 88

Administration of PRO instruments will be performed according to the validated procedure and guidelines of each respective instrument, except for some assessments for exploratory analyses.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 36, 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100X.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine 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). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 HLA TYPING

HLA testing will be performed on PBMC from any single blood sample collected for immunogenicity analysis. If the subject has a record of previous high resolution HLA testing and access to the results, then HLA testing is not required.

The DNA extracted from the blood sample will be used to determine if alleles at the MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at the screening, Day 0, Weeks 15, 28, 36, 62, 88 and read in a central laboratory. HPV PCR by Cobas™ HPV test will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer at Day 0, Weeks 15, 28 or 36, the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples to eliminate potential interference with the results of HPV testing.

At visits where multiple cervical samples are collected, the two Digene cervical brushes will be collected prior to the ThinPrep™ sample. Details of sample collection and shipment information will be provided in laboratory manual.

6.13 COLPOSCOPY AND CERVICAL BIOPSIES

Colposcopy at screening must be adequate, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected dysplasia. An ECC is not required for study entry. However, if an ECC was done as part of routine care during the screening period, and found to have evidence of cervical HSIL such subject should not be enrolled in the study. Colposcopy is not required to be performed at screening if adequate colposcopy was previously obtained upon collection of initial biopsy. All colposcopies performed after informed consent must be conducted according to the procedures outlined in Appendix C.

Interval colposcopies will be performed at Day 0, Weeks 15, 28, 36, 62, and 88. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

Digital photographs of the cervix will be captured during each colposcopic examination to document the clinical findings. If a biopsy or surgical excision is performed, images of the cervix should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach and 2) the process for uploading the images to a secure

server. Additionally, after subject is enrolled if vaginal or vulvar lesion should develop, photograph should be taken to document the clinical exam finding.

6.13.1 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at screening to confirm eligibility. If the criteria outlined in Table 5 or 6 are met, ectocervical biopsies may also be performed at Week 36 to provide tissue for histopathologic assessment of disease regression.

Biopsies should not be performed at any other visit unless there is suspicion of disease progression. Removal of additional tissue by biopsy before Week 36 will bias results toward improvement regardless of whether the subject is in the active or placebo group. The bias introduced will obviously be more significant for smaller lesions. For this reason, if biopsies are obtained prior to Week 36, the subject will be treated as a non-regressor. Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy prior to Week 36, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.13.2 UNSCHEDULED BIOPSIES

In the event unscheduled biopsy is performed prior to Week 36, subject will be considered as non-responder. The subject will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and Investigator's judgement based on results of histological diagnosis from unscheduled biopsy Additional instructions for collecting ectocervical biopsies are detailed in Appendix C. All biopsy samples/excised tissue will be sent to the PAC for review.

6.14 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

6.15 RESTRICTIONS

6.15.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled otic and ophthalmic corticosteroids are allowed
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine
- Blood thinners/Anticoagulants within 2 weeks of any study treatment

6.15.2 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy; see Section 7.1.9 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not

result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;

- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.2.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.
Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.3 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable

regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.4 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

7.1.5 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported.

The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)

The investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.6 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the investigational device. An AE may also be assessed as not

related to the IP and/or the investigational device. Because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the investigational device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event.

7.1.7 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs

- Is judged by the investigator as clinically significant

7.1.8 POST-STUDY REPORTING REQUIREMENTS

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol-required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.9 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor study team and medical monitor within 24 hours after learning of the pregnancy. The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject. Subjects who are not withdrawn will continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF THE COLLECTION AND RECORDING OF SAFETY DATA

Non-serious AEs and SAEs (and UADEs) will be collected for each subject from the time when informed consent is obtained through Week 88.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.

3. Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE (or UADE) occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 EVENTS REQUIRING EXPEDITED REPORTING

Events requiring expedited reporting (ERER) will be defined as related adverse events due to VGX-3100X/placebo delivered with CELLECTRA™ 5PSP that meets any of the following criteria:

- Grade 3 or greater administration site erythema, and/or induration recorded ≥ 2 hours after Study Treatment
- Grade 4 or greater administration site pain, tenderness recorded ≥ 2 hours after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

As per the Toxicity Grade for Healthy Adults and per CTCAE v 4.03. The most severe grade for that particular event is to be documented in the CRFs.

Sites will inform the Sponsor vial email and to designee vial phone or fax of any ERER within 24 hours to discuss whether further dosing should continue by contacting Inovio as follows.

EMAIL: Safety@inovio.com
SAFETY FAX: [redacted] or [redacted]
SAFETY PHONE: [redacted]

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

- If at any time during a study one-third (1/3) or more of the subjects experience an ERER, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB. Only the DSMB may review unblinded data in making their recommendation to the Sponsor regarding continuation of a trial.
- If any SAE (or potentially life-threatening AE), or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study, experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

The sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

8 STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects with a histologic diagnosis of cervical HSIL. The study's primary endpoint is binary: regression to CIN1/normal and clearance of HPV-16 and/or HPV-18 infection from cervical tissue based on tissue collected at Week 36. The primary hypothesis is that VGX-3100X will be superior to placebo regarding the proportion who achieve the primary endpoint. Secondary efficacy analyses involve regression to CIN1/normal, clearance of HPV-16 and/or HPV-18 infection from cervical tissue and non-progression of cervical lesions. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, clearance of HPV-16 and/or HPV-18 infection from non-cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, and virology and efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized (2 VGX-3100X:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) BMI category ($\leq$25 vs. >25 kg/m^2), and c) age category (<25 years vs. $\geq$25 years). There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The study is double-blinded.

8.3 SAMPLE SIZE/POWER

A sample of 165 subjects will be randomized to receive either 6 mg VGX-3100X or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100X superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 40% and 15% for VGX-3100X and placebo, respectively, and assuming 90% evaluability from randomization. These assumptions are based on the mITT result from the Phase 2 study.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be primary for the analysis of efficacy in this study.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

Subjects who do not complete the study will not be replaced.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment arm for all randomized subjects and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the mITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the mITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true population probabilities of the primary endpoint for VGX-3100X and Placebo, respectively. The primary hypothesis of superiority is:

$$H_0: \delta \leq 0 \textit{ vs. } H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [27]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

The secondary efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. It also includes subjects who underwent early intervention prior to this time frame; these subjects are considered as failures for the efficacy endpoints. Table 13 provides details for the definition of the primary endpoint response.

Table 13. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 or HPV-18 at Week 36 AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

Exploratory analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) colposcopy results, c) cytology results, and d) HPV results. As each of these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

Other exploratory analyses will examine durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue at Weeks 62 and 88, and clearance of HPV-16 and/or HPV-18 infection from non-cervical tissue. Descriptive statistics will be utilized; percentages of subjects who cleared will be presented by time point or anatomic location and treatment group.

8.10 IMMUNOGENICITY ANALYSES

Post-baseline cellular and humoral response magnitude may be compared between treatment groups using a difference in medians and associated non-parametric 95% CI. Post-baseline tissue response magnitude will be compared between treatment groups using a difference in means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach

with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [27]. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

Any AEs with a missing or partial onset date will be included in the overall AEs, but not be included within specified day-range summaries. AE duration will be calculated as (Stop Date – Start Date) + 1.

8.11.2 LABORATORY DATA

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

8.12 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

8.13 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the mITT population.

8.14 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes among subjects who receive VGX-3100X will be compared between those with excision versus those without excision, based on PRO endpoints. This comparison will utilize the median difference in endpoints or the difference in proportions of subjects with endpoints and associated non-parametric or Miettinen and Nurminen [27] 95% CIs, for continuous responses and binary responses, respectively.

8.15 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

A subject's regression outcome is missing if her CIN grade and HPV clearance at Week 36 cannot be determined. Any subject who had suspected disease progression before Week 36 will be considered a non-regressor regardless of the Week 36 result, even if missing.

8.16 INTERIM ANALYSIS

No formal interim analyses will be performed for this study. For reasons of futility (early evidence of poor efficacy of VGX-3100X) or safety issues, the DSMB could recommend stopping enrollment at any time. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

9 DATA COLLECTION, MONITORING AND REPORTING

9.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

9.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. This retention period may be superseded by applicable regulatory requirements (e.g. minimum of 25 years for Health Canada). The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.4 SAFETY AND QUALITY MONITORING

9.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100X group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB

review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

9.4.2 PATHOLOGY ADJUCATION COMMITTEE

All cervical biopsies will be read by a central expert Pathology Adjudication Committee (PAC) to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of three pathologists. Each specimen will be read by two pathologists independently in a blinded fashion. If the two pathologists agree the reading will be considered the clinical disease status for the subject. If the readings of the first two pathologists are discordant, the third pathologist will review and if there is agreement among any of the three readings, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached. A fourth pathologist will be identified to support the PAC in the event that one of the other pathologists is absent.

9.4.3 CLINICAL MONITORING

Clinical Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
    - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
    - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Assure that the study facilities continue to be acceptable
    - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

9.5 ADVERSE EXPERIENCE (AE) REPORTING

To assure the safety of the subjects, information about all AEs (see Section 7.1), whether volunteered by the subject, discovered by investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

9.5.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the AE CRF. Safety events will be analyzed and summarized throughout the study. Emphasis will be placed on the following:

- Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately
- Unsolicited AEs, SAEs or UADEs will be collected and summarized for the entire study period

9.5.2 STUDY REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol. An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.3 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.4 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy. At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION

EMAIL: Safety@inovio.com
SAFETY FAX: [redacted] or [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms and any supporting documents to the Sponsor is as an attachment to an e-mail message, to the email addresses as indicated above and by facsimile (Fax), to include a fax coversheet that identifies the reporter and contact information to the designee.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Event
- Study number
- Subject number (SID) and initials
- Investigational Device serial number
- Lot numbers
- Reporter name and contact information

In the case of a "minimum report" (one that is solely comprised of the information bulleted above), a more detailed follow-up report will be sent as soon as more information becomes available but no later than 5 calendar days after the date of the initial report. The investigator will supply the Sponsor and the IRB with any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

9.5.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.3 and 7.1.4).

9.5.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint is defined as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution." All product complaints that meet this definition must be reported to the sponsor with 10 days of discovery

A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled.

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting form must be completed and emailed to the Sponsor at [redacted] as shown in Appendix B.

9.6 STUDY DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

10 ETHICS

10.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2 INSTITUTIONAL REVIEW BOARD OR INSTITUTIONAL ETHICS COMMITTEE (IRB/IEC)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/IEC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/IEC as required.

- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/IEC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

10.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

11 PROTECTION OF HUMAN SUBJECTS

11.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

11.2 COMPLIANCE WITH IRB/IEC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator must be provided to Sponsor.

11.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

11.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

11.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Device used in this study however will be asked to complete a participant diary card during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

11.6 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the sponsor in all participating countries and is fully supporting the study. Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted.

13 PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

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15 APPENDICES

15.1 APPENDIX A: PARTICIPANT DIARY CARD

Subject Diary

HPV-301

Subject #: _____

Injection Date:_____

Note to Participant:

For questions or problems, please contact your Site Coordinator.

Name: _____

Telephone: (_____) _____

Email (optional): _____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

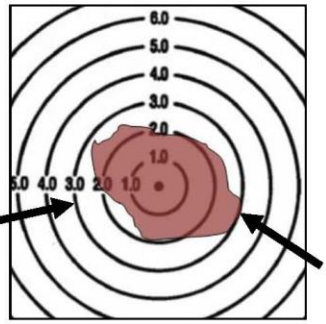
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 0: Evening of Injection Subject #: _____ Date: _____/_____/_____

Sometime during the evening on the day you were injected, fill out the information below. The items on this page refer to the time from your injection to 11:59 p.m. on the day of injection (Day 0). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst the symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 2.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

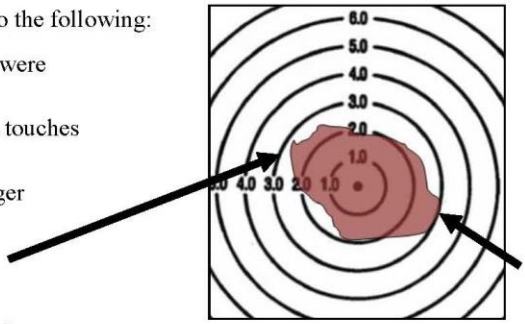
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 1: 1 Day After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 1). If any of the information changes after you fill out this page but before 11:59 p.m. tonight make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 4.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

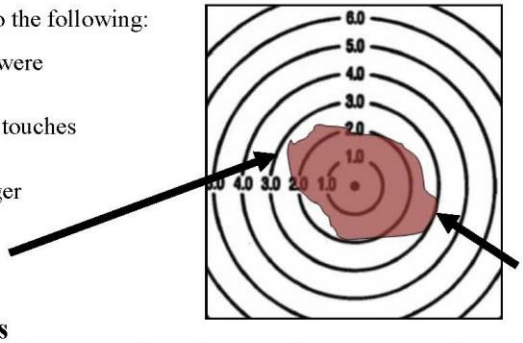
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 2: 2 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 2). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describesyour worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 6.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

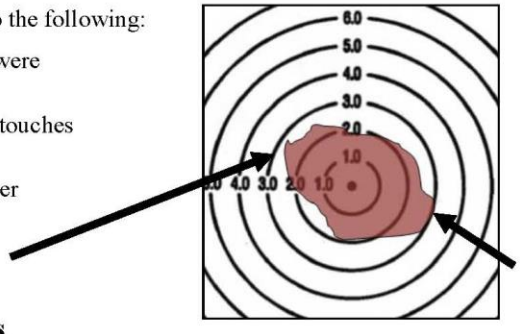
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 3: 3 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 3). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m.tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 8.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

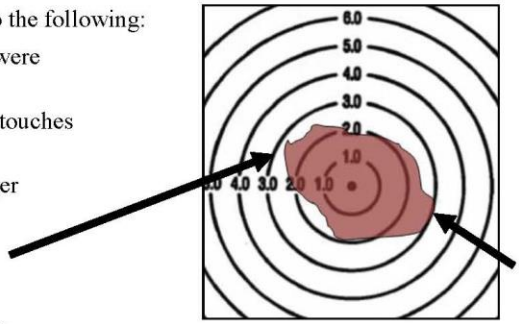
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 4: 4 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 4). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 10.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

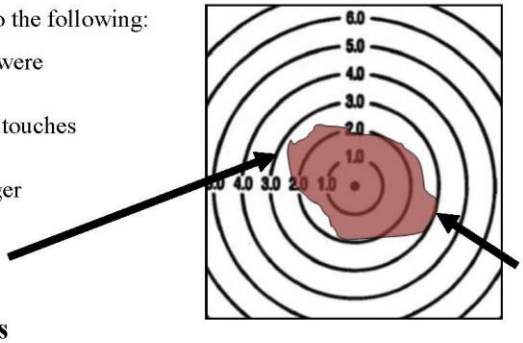
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 5: 5 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 5). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 12.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

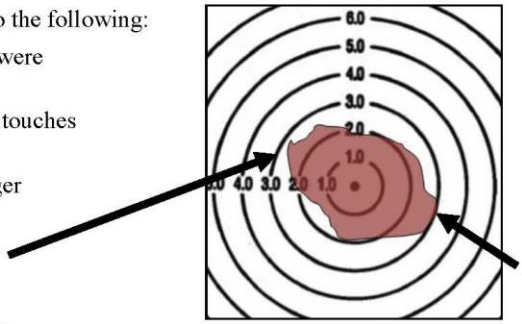
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 6: 6 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 6). If any of the symptoms you reported on previous pages have not gone away ("resolved"), you will need to let the Site Coordinator or Doctor know.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 14.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

15.2 APPENDIX B: ERROR REPORTING FORM

inovio
PHARMACEUTICALS

CELLECTRA® 5PSP Device Error Form

Please complete the form and fax to (267) 440-4242 or scan the form to [redacted]

Protocol#_____ **Site#** _____ **Subject ID** _____ **Week#**_____ **Visit Date**_____

DEVICE INFORMATION

CELLECTRA® 5PSP Base Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the front cover

CELLECTRA® 5PSP Handset Serial No ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the handle

CELLECTRA® 5PSP Array Lot No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the package

Time of Treatment: _____

Type and Location of Treatment: ☐ **IM** ☐ **ID**
☐ **R**ight Arm ☐ **L**eft Arm
☐ **L**eft Quadriceps ☐ **R**ight Quadriceps
☐ Other Location, specify:_____

IM-5P ONLY, was the EP Guide used? ☐ YES ☐ NO

If EP Guide was used, please provide reason and include subject's BMI.

Was injection successful? ☐ YES ☐ NO

If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read EP successful? ☐ YES ☐ NO

If NO, please check all complications that led to failure and describe complication below

☐ Impedance Test Error message displayed, fill out Impedance Test Error section below
☐ Electroporation Error message displayed, fill out Electroporation Error section below
☐ EP aborted by trigger or keypad error message displayed
☐ Battery level too low for electroporation message displayed
☐ Difficulty inserting array into muscle or skin
☐ Other, please specify below

Describe device complication below (continue on back if necessary):

Total # of arrays used: _____ **Total # of attempts:** _____

Impedance Test Error (IM-5P Only)

Was the array fully inserted in subject's arm? (or thigh as applicable) ☐ YES ☐ NO
Were all attempts performed on the same day? ☐ YES ☐ NO
Was a different location used for each attempt? ☐ YES ☐ NO
Was a new array used for each attempt? ☐ YES ☐ NO

Please provide any additional information below (continue on back if necessary):

Electroporation Error

Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many_____
Was the array fully inserted in the subject's arm? ☐ YES ☐ NO
Was the array inserted perpendicular to the subject's skin? ☐ YES ☐ NO
Did the needles of the array appear damaged in any way? ☐ YES ☐ NO

If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.

Please provide any additional information below (continue on back if necessary):

15.3 APPENDIX C: GUIDELINES FOR COLPOSCOPY, BIOPSY, AND SURGICAL EXCISION

Colposcopy Procedure

It is recommended that all study colposcopies performed after informed consent be according the procedures recommended by the American Society of Colposcopy and Cervical Pathology (ASCCP):

1. Use warm, clean water to lubricate the vaginal speculum. Avoid other lubricant substances which could obscure results.
2. If the vaginal walls are lax, a lateral vaginal sidewall retractor aligned perpendicular to the speculum may facilitate visualization.
3. Examine the cervico-vaginal secretions and remove any excess mucus from the cervix with saline-soaked cotton swabs.
4. Obtain any required specimens required for cytology and HPV testing.
5. Using low-power magnification (5x to 10 x) inspect the cervix for obvious areas of abnormalities.
6. Swab or spray the cervix with 3-5% acetic acid. Reapply every 2-3 minutes during the examination.
7. Use the green or blue filter to examine blood vessels. Increase magnification (15x)
8. Identify the distal and proximal boarders of the transformation zone.
    a. The inner border is the entire 360-degree circumference of the squamocolumnar junction
        i. If the junction is proximal to the external os, in the canal, use a cotton-tipped applicator to pry either the anterior lip up or the posterior lip down or use an endocervical speculum
        ii. If the junction is not visualized in its entire circumference, the colposcopy is deemed inadequate
    b. The distal limit of the transformation zone may be identified by finding the most distal crypt openings or nabothian follicles in the lips of the cervix and drawing an imaginary line connecting these landmarks
9. Inspect the entire new squamocolumnar junction and detect and evaluate any abnormal areas.
10. Evaluate the upper third portion of the vagina.
11. Lugol or Schiller's solution may be applied to further define previously identified lesions.

Cervical Biopsies

Endocervical Curettage

ECC is to be performed using a kervorkian curette or equivalent instrument. Rotate and scrape the curette 360° in the endocervical canal and use a cytobrush to remove the specimen. Deposit the specimen onto a Telfa pad before depositing in the specimen vial containing 10% neutral buffered formalin solution and labeled with the subject identification (SID) number.

Ectocervical Biopsies

Ectocervical biopsies should only be performed prior to Week 36 if disease progression is suspected. Only the suspect lesion should be biopsied in that circumstance.

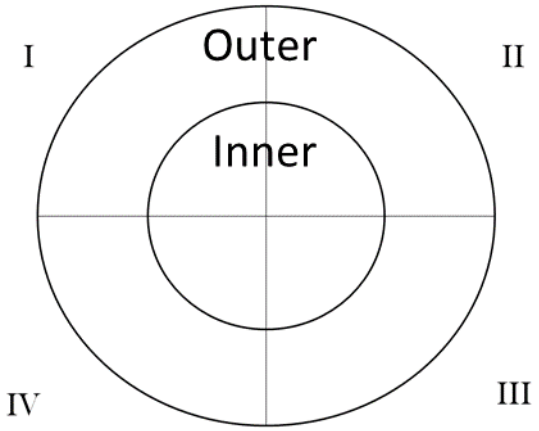
If the subject is eligible for 4 quadrant biopsy at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the subject's ID number and the quadrant number according to the figure below.
2. Perform and record colposcopy findings from each quadrant according to the following categories

a. Negative (no lesion present)
b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
d. Suspicion of invasive cancer
e. Invasive cancer

3. Perform colposcopic directed biopsies from all quadrants with lesions.
4. Multiple biopsies can be obtained of a lesion at the discretion of the investigator but must be uniquely labeled
5. If a quadrant is free of lesions, obtain a random biopsy at the squamocolumnar junction in that quadrant at 2, 4, 8, or 10 o'clock.
6. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Figure 1 – Biopsy Quadrant Numbers



Surgical Excision

For subjects undergoing surgical excision at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the SID number and the specimen type.
2. Record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform the LEEP or CKC per usual practice.
4. Specimen should be marked at 12 o'clock with suture or gentian violet ink for purposes of orientation
5. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

15.4 APPENDIX D: EQ-5D-5L HEALTH QUESTIONNAIRE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

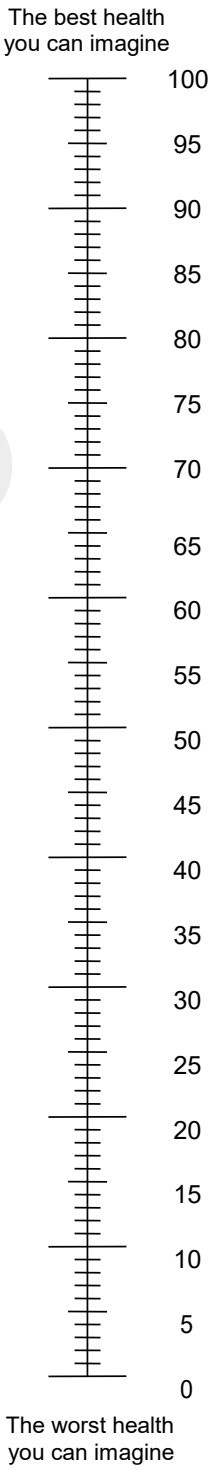
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



15.5 APPENDIX E: SF-36 V2 QUESTIONNAIRE

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

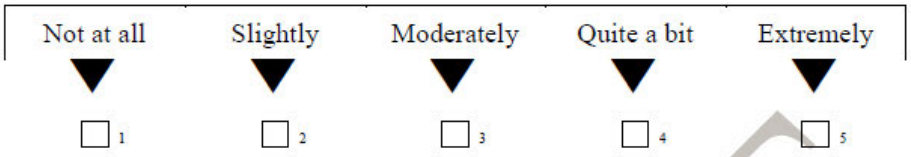
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

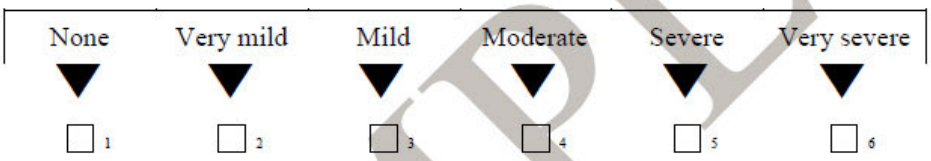
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

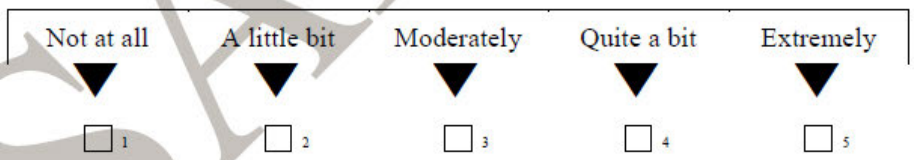
6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much bodily pain have you had during the past 4 weeks?**



8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

HPV-301
REVEAL I Trial (Randomized Evaluation of VGX-3100X and Electroporation for the treatment of Cervical HSIL)

A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100X 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)0F1 of the Cervix

Protocol Version 2.1
10-JUN-2016

Written by:

[redacted]

[redacted]

[redacted]

Date (DD-MMM-YYYY)

Biostatistician

[redacted]

Date (DD-MMM-YYYY)

Medical Monitor

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

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Protocol Version 2.1
10-JUN-2016

Written by:

[redacted]

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Reviewed and Approved by:

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Date (DD-MMM-YYYY)

Biostatistician

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Date (DD-MMM-YYYY)

Medical Monitor

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[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

[redacted]

Date (DD-MMM-YYYY)

HPV-301

REVEAL 1 Trial

(Randomized Evaluation of VGX-3100 and Electroporation for the Treatment of Cervical HSIL)

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

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

EudraCT #2016-002761-63

Version 3.0

23 September 2016

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

Short Title: REVEAL 1 Trial (Randomized Evaluation of VGX-3100 and Electroporation for the treatment of Cervical HSIL)

Biological Product: VGX-3100

Protocol Number: HPV-301

Sponsor: Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462

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Inovio Pharmaceuticals, Inc.

SUMMARY OF CHANGES

The following is a list of significant protocol changes from HPV-301 protocol version 2.1 dated 10 June 2016 to HPV-301 protocol version 3.0 dated 23 September 2016. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol.

1. Name of the investigational product has been changed from VGX-3100X to VGX-3100. The term VGX-3100 as used in this document denotes 3.0 ± 0.2 mg/mL pGX3001 bulk plasmid and 3.0 ± 0.2 mg/mL pGX3002 bulk plasmid in saline sodium citrate (SSC) buffer, refrigerated formulation
2. The primary analysis for the study has been changed from modified-intention-to-treat (mITT) based on complete data to intention-to-treat (ITT) analysis. Based on this change, the number of subjects to be enrolled in the study is now 198 instead of 165
3. The following modification have been made to the objectives and endpoints:
    a. Changed the exploratory objective of "clearance of HPV-16 and/or HPV-18 infection from anatomic location outside the cervix" to secondary objective
    b. Added association of microRNA profile to the exploratory objective
    c. Specified the countries where patient reported outcome will be collected in the exploratory endpoint
4. The following modification have been made to inclusion and exclusion criteria:
    a. Inclusion criteria 10c) clarified the duration of use of contraceptive method from screening until week 36
    b. Exclusion criteria 4 has been modified to remove the treatment of genital warts within 4 weeks of screening
5. The following modification have been made to the study evaluation:
    a. Added an additional in-person visit to allow collection of samples for HPV typing by cobas™ HPV test and mircoRNA profile test
    b. Changed the method of collection from peri-anal to intra-anal swab
    c. Removed the collection of non-cervical samples (i.e. oropharyngeal rinse, vaginal and intra-anal samples) at Week 15 visit
    d. Additional time-points for patient reported outcome questionnaire completion at Weeks 4, 12 and 36 visits
    e. Removed collection of digene swabs at Week 62 visit
    f. Specified collection of weight at Day 0, Weeks 4 and 12 to align with collection of BMI data for study treatment purposes
    g. Clarified socio-behavioral assessment at Weeks 36 and 88 will include data collection of any change from screening
6. Section 2.1.3 Definition of responder and non-responder has been modified to include additional category in definition of non-responder
7. Added information on supplementation of subjects in case more than 10% of subjects from randomization of the study treatment discontinue prior to the Week 36 primary endpoint procedure
8. Section 5.7 Return and destruction of investigational product has been updated to clarify process for destruction and return of unused investigational product

9. Section 6.1.1 Screening evaluation has been updated to include the information on subjects that can be qualified for screening into the study
10. Section 6.15.1 Prohibited concomitant medication and treatment has been updated to add the restriction of use of any Blood thinners/anticoagulants, aspirin or other medication that affect blood clotting should not be taken X days prior to undergoing biopsy or surgical excision
11. Added reporting of progression of HSIL to microinvasive or invasive squamous cell carcinoma as an SAE
12. Section 7.3.1 has been modified to replace the term "Events requiring expedited reporting" to "Adverse events of special interest". Added clarification on reporting requirements to sponsor
13. Section 7.4.2 has been updated to reflect change in reporting contact details in event of SAE
14. Section 8 Statistical analysis section has been modified to reflect that missing data will be considered as a failure for ITT efficacy analysis. A subgroup analysis for primary and secondary efficacy endpoints will be performed by history of exposure to prophylactic HPV vaccine.
15. Section 9.4.2 Pathology adjudication committee section has been updated to clarify in case of disagreement between first two pathologists, the third pathologist will review the histology slides independently. Also, if there is disagreement across all three pathologist, worst diagnosis will be reported as clinical disease status for the subject.

PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Investigator below constitute his/her approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, ICH-GCP guidelines, local legal and regulatory requirements as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____

Investigator – Signature Date (DD/MMM/YYYY)

_____

Investigator – Printed Name

Site Number: _____

Site Name: _____

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I LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
Baseline	Prior to first dose
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CMI	Cell mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation with CELLECTRA™ 5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion

HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LSIL	Low grade squamous intraepithelial lesion
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection

TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

II CLINICAL PROTOCOL SYNOPSIS

Title of Study: 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)[1] of the Cervix	
Estimated Number of Study Centers and Countries/Regions: Approximately 125 Sites in up to 25 Countries	
Study Phase: 3	
Primary Hypothesis: Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL[Cervical Intraepithelial Neoplasia (CIN)2, CIN3] of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit	
Study Drug Dose	6 mg (1 ml)
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device
Schedule	Day 0, Week 4, and Week 12 study visits
No. of Subjects	Approximately 198 subjects will be randomized in a 2:1 ratio to receive VGX-3100 or placebo
Study Duration	88 weeks
Primary Objective	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**
Primary Endpoint	Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsy or excisional treatment) and **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit

[1] Terminology based on 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP)

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of serious adverse events and Unanticipated [Serious] Adverse Device Effects for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by **virologic clearance of HPV-16 and/or HPV-18**	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by **complete histopathologic regression of cervical HSIL to normal**	4. Proportion of subjects with **no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both **complete histopathologic regression of cervical HSIL to normal and virologic clearance** of HPV-16 and/or HPV-18	5. Proportion of subjects with **no evidence of LSIL or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) **and no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Week 36 visit
6.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic non-progression**	6. Proportion of subjects with **no progression of cervical HSIL** to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response following administration of VGX-3100 compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 8c. Flow Cytometry response magnitudes at baseline and Week 15 visits

Exploratory Objectives	Associated Exploratory Endpoints
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Evaluate effect of Human Leukocyte Antigen (HLA) type on efficacy	2. HLA (per-locus and per-allele basis) in conjunction with **histologic regression of cervical HSIL** at Week 36 visit
3. Describe association of microRNA (miRNA) profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	3. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits) and miRNA profile (baseline, Week 8) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe the durability of **virologic clearance of HPV-16 and/or HPV-18** for subjects treated with VGX-3100 compared with those treated with placebo	4. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Weeks 62 and 88 visits
5. Describe the patient-reported outcomes for subjects treated with VGX-3100	5. Patient-reported outcome questionnaires self-administered at baseline, after each dose at Weeks 4, 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK

Study Design:

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled Phase 3 study to determine the efficacy safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16 and/or HPV-18 (HPV-16/18). The composite primary endpoint is histologic regression of cervical HSIL, and clearance of the underlying HPV-16/18 infection. A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

To be eligible for the study, women age 18 years and above must consent to participate and have biopsy/biopsies of the cervical lesion(s) at the time of screening. The biopsy slides are sent to central

pathology lab for Pathology Adjudication Committee (PAC) review in a blinded manner to establish the presence of cervical HSIL (CIN2, CIN3) prior to enrollment. Subjects must also have a cervical ThinPrep™ specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

All eligible subjects will receive three doses of VGX-3100 or placebo administered IM followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment is administered on Day 0, the second at Week 4, and the third (final) study treatment is administered at Week 12. The first dose is administered as soon as possible following confirmation of the cervical HSIL diagnosis and cervical sample positive for HPV-16/18 but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening.

Subjects are randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) Body Mass Index (BMI) category ($\leq$25 vs. >25 kg/m^2), and (c) age category (<25 years vs. $\geq$25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The long term follow up plan following the Week 36 efficacy assessment will include safety, cytology and HPV testing for a period of approximately 1 year (Week 88).

Efficacy: Visualization of a normal appearing cervix by colposcopy and cytology are insufficient evidence to confirm disease regression. Therefore, disease regression will be based on histopathological assessment, which is considered the definitive method for diagnosis. Subjects will also be assessed by colposcopy, cytology, and HPV testing at screening, and at specified visits on and after Day 0. Digital photographs of the cervix following application of acetic acid will also be used to document colposcopic exam findings.

Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (e.g. loop electrosurgical excision procedure (LEEP), large loop excision of transformation zone (LLETZ), cold knife conization (CKC)) or by biopsy (4 Quadrant Biopsy or 4 Quadrant Biopsy with Endocervical Curettage (ECC)) based upon the assessment at Week 28 of cytology, High Risk (HR) HPV status, and colposcopic findings (see Tables 5 and 6, for Minimally Required Procedures).

Safety: All subjects will be followed for 88 weeks.

Subjects will be monitored for:

1) Local and systemic events for 7 days following each investigational treatment as noted on a Participant Diary Card (PDC);
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

Data and Safety Monitoring Board (DSMB): The DSMB will meet quarterly to review unblinded safety data and histopathologic regression results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with histopathologic regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed.

Immunogenicity: Humoral and cell mediated immune responses in response to VGX-3100 treatment may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

Virology: Cervical cytology samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 8, 15, 28, 36, 62, and 88 by cobas™ HPV test. Additionally, if there is residual tissue in the paraffin block from cervical tissue after histologic diagnoses have been rendered at screening and Week 36, then unstained slides and/or the relevant paraffin blocks may be tested for the presence of HPV-16/18. Vaginal brush and oropharyngeal rinse samples will be obtained at Day 0 (prior to dosing), Weeks 36 and 88 while intra-anal samples will be obtained on Day 0 (prior to dosing) and Week 36 to characterize HPV infection.

HLA typing: The relationship between subject HLA types and efficacy responses will be explored using available PBMC sample collected for immunogenicity analysis.

Study Population

Inclusion Criteria:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas™ HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable :
        - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal

contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
    - Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
    - Intrauterine device or intrauterine system;
    - Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject

11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

Exclusion Criteria:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
3. History of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant during the study;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
7. Presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 or less than Grade 1 but deemed clinically significant by the investigator within 30 days prior to Day 0;
8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 30 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results;
9. Receipt of any non-study, non-live vaccine within 2 weeks of Day 0;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or

endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

12. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Table 1. Schedule of Events

Tests	Screening (-10 wks to -1 Day)	Weeks												
		Day 0	8-14 days post Day 0 Phone Call	4 (± 4 days)	8-14 days post Wk 4 Phone Call	8 (± 4 days)	12 (± 4 days)	8-14 days post Wk 12 Phone Call	15 (± 1 week)	28 (± 1 week)	36 (± 1 week)	40 (± 2 weeks) Phone call	62 (± 2 weeks)	88 (± 2 weeks)
Informed consent	X													
Medical History	X													
Demographics	X													
Socio-behavioral[a]	X										X			X
Inclusion / Exclusion	X	X												
Randomization		X												
Physical examination[b]	X	X		X		X	X		X	X	X		X	X
Vital signs	X[c]	X		X		X	X		X	X	X		X	X
Screening safety[d]	X													
Pregnancy Test[e]	X	X		X			X		X	X	X		X	X
HIV Antibody Testing	X													
Blood immunologic samples[f]	X	X				X			X[g]		X			X
ThinPrep™ [h,i]	X	X				X			X	X	X		X	X
Cervical Digene swabs[i,j]	X	X							X	X	X			X
Colposcopy, lesion photography[k]	X[l]	X							X	X	X		X	X
Ectocervical biopsy[m]	X										X[n]			
Surgical excision[m]											X[n]			
OP rinse, vaginal swabs		X									X			X
Intra-anal swabs[o]		X									X			
Inject VGX-3100/Placebo		X		X			X							
Post treatment assessment		X	X	X	X	X	X	X[q]	X					
Distribute PDC		X		X			X							
Review PDC			X		X	X		X[q]						
PROs[p]		X	X	X	X		X	X[q]		X	X	X		X

[a] Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

[b] Full physical examination (PE) mandatory at screening and study discharge (Week 88), otherwise targeted physical assessment as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

[c] Screening vital signs must include a measured height and weight. Weight will be collected on Day 0, Weeks 4 and 12;

[d] Screening safety includes 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 30 days prior to Day 0;

[e] Negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

[f] At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood and 8 mL serum per time point (a total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0). HLA testing will performed once from an existing PBMC sample;

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

[i] Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

[j] Collected prior to the ThinPrep™ sample;

[k] Acetic acid should be applied to the cervix then photographs of the cervix and the associated lesion should be collected prior to and after biopsies and at all colposcopic examinations;

[l] Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy ;

[m] Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 5 and 6);

[n] Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from screening and/or Week 36 specimen(s) (paraffin blocks or unstained slides) may be used for immunohistochemistry (IHC) and HPV testing;

[o] To be collected only if subject consents for intra-anal sample collection

[p] One or both PRO questionnaires (i.e. SF-36 and EQ-5D-5L) will be completed by subjects enrolled in US, Canada, Mexico, Germany and UK at multiple visits during the study. Refer to Section 6.8 for details

[q] Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 HPV INFECTION, CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a HR HPV type [2, 3]. Up to 13000 women in the US alone are diagnosed with cervical cancer each year, which leads to an estimated 4120 deaths [4]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two genotypes are estimated to cause about 70% of all cervical cancers [5, 6].

Incident infection by HPV is characterized by ongoing viral replication and shedding and is associated with early histologic changes (grade 1 cervical intraepithelial neoplasia) when the female cervix is infected with HPV. Most cases of genital HPV infection clear spontaneously, but persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions of the cervix, HSIL which is inclusive of grade 2 and 3 cervical intraepithelial neoplasia (CIN2/3) [7]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [8, 9]. The basis for these changes are attributed to the viral proteins E6 and E7. Infected cells produce E6 and E7 constitutively which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia.

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade CIN caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [10]. This means that the large number of women who already have high grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they didn't respond to vaccination, must currently only rely upon surgery and the chance of spontaneous regression to treat their condition and avoid progression to cancer. Furthermore, the number of US-eligible teenagers who complete the prophylactic vaccination series remains low; 39.7% of US girls ages 13-17 completed their prophylactic HPV immunization series in 2014, which leaves a potentially vulnerable, under-protected population [11]. The current approaches to the management of cervical HSIL typically require surgery (i.e. LEEP/LEETZ, laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100 is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

1.1.2 VGX-3100

VGX-3100 contains plasmids that target HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was water for injection with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This WFI/LGS formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100[2] was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This SSC formulation of VGX-3100 was administered to 116 subjects in a Phase 1 clinical trial, HPV-101. In study HPV-101, three 6 mg doses of VGX-3100 as the SSC formulation were delivered IM followed by EP with CELLECTRA™ 5P to healthy adults. Based upon interim analysis data at study Week 14, the SSC formulation is considered non-inferior to the WFI/LGS formulation based upon a 2-fold rise in overall Spot Forming Units (SPU) to the antigens encoded by the plasmids per 10^6 Peripheral Blood Mononuclear Cells (PBMC) as measured from baseline to Week 14 using the interferon-γ ELISpot assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (WFI/LGS formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or HPV-18. The Phase 2b study, HPV-003, enrolled 167 subjects with high grade cervical dysplasia from seven countries and one United States Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, United States and Puerto Rico). Subjects were randomized in a 3:1 ratio to the treatment arm (VGX-3100, WFI/LGS formulation) or the placebo arm, respectively. All subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to CIN1 or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol and modified intent to treat analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.3 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses

[2] Designated in earlier version of the HPV-301 protocol as VGX-3100X

creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity

[12, 13]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [14, 15]. This technology has been used for more than three decades by molecular biologists for cell transfection and has demonstrated versatility in use, as shown by its functionality in combination with a range of molecules, tissue types, disease indications, and across species [16].

The CELLECTRA™ device developed by Inovio is used for investigational purposes to administer plasmid-based DNA, in both prophylactic and therapeutic settings. Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency, and has demonstrated that the device helps to elicit favorable immunogenicity in several species (e.g., mice, pigs, and rhesus macaques) [17, 18].

VGX-3100, WFI/LGS formulation, has been administered throughout Phase 1 and Phase 2 investigations with the CELLECTRA™ 2000 device. A next generation device, CELLECTRA™ 5PSP, will be used in Phase 3. Both designs of the CELLECTRA™ device enhance the intracellular uptake of VGX-3100 by the delivery of electrical current, and the electrical current delivery and pulse pattern (electroporation) is identical in both designs. CELLECTRA™ 2000 involves a manual injection of VGX-3100 while the CELLECTRA™ 5PSP device will automate the intramuscular delivery of VGX-3100 and delivery of the EP pulses triggered by a single button press. Neither the dosage nor volume of VGX-3100 administered differs between the two devices. Administration of VGX-3100 with the CELLECTRA™ 5PSP also allows selection of the array needle length (13, 19 or 25 mm) depending on the estimate of the recipient's subcutaneous fat and muscle tissue.

The technology differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design (Table 2) are not significant and do not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, environmental specifications, and sterilization or performance specifications. The material changes are to the outer housing of the device and not to patient-contacting materials.

Table 2. Comparative Device Overview

	CELLECTRA™ 5PSP	CELLECTRA™ 2000
Array Specifications		
Electrode Number and Material (no bore)	5 Stainless steel, 304 electrodes pentagonal arrangement	5 Stainless steel, 304 electrodes pentagonal arrangement
Electrode Length	1.555 ± 0.020" (39.5mm)	1.555 ± 0.020" (39.5mm)
Electrode Gauge	22 Gauge (0.0278-0.0280 inch diameter)	22 Gauge (0.028±0.001 inch diameter)
Electrode Trocar Tip	15 ± 2°	15 ± 2°
Array Housing	Bayer Makrolon 2458C and Loctite 3921	GE Plastics (Sabic) Lexan HPS2
Sterilization Method and Sterility Assurance Level (SAL)	Gamma Irradiation 25-40kGy SAL 10^{-6}	Gamma Irradiation 25-40kGy SAL 10^{-6}
VGX-3100 IM Injection Method	Automated (Handset mediated)	Manual (needle and syringe)
Injection Needle Material (full bore)	Stainless steel, 304	Stainless steel, 304
Injection Needle Length	2.102 ± 0.020" (54.4mm)	2.0" hypodermic needle recommended
Injection Needle Gauge	21 Gauge (0.03250-0.03200 inch diameter)	21 Gauge
Injection Needle Trocar Tip	15° (double ended)	15° (single ended)
VGX-3100 IM Injection Depth	13, 19 and 25 mm	13,19 and 25 mm
VGX-3100 IM Injection Volume	1.0±0.1mL	1.0±0.1mL
Electroporation Parameters		
Voltage delivered to subject tissue	40-200 V maximum (varies with subject tissue impedance)	40-200 V maximum (varies with subject tissue impedance)
Pulse Width	52 milliseconds (ms)	52 milliseconds (ms)
Pulse Current	0.5 A; 1.0 A max	0.5 A ; 1.0 A max
Maximum Phase Charge	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses	Maximum Delivered Charge = 78mC (max) = 0.5A x 0.052 seconds x 3 pulses
Frequency	Pulses initiated at 1.0 second intervals	Pulses initiated at 1.0 second intervals

Benchtop design verification testing and a non-significant risk device functionality study will be completed prior to Phase 3 to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™ 5PSP device design meeting its safety and performance specifications, and no change to the administration of VGX-3100 by electroporation. Inovio's device experience demonstrates that delivery of electroporation pulses into muscle immediately following injection of DNA plasmids is well-tolerated in humans and no significant safety issues have been identified [19-21].

1.1.4 SELECTION OF STUDY DESIGN

This Phase 3 study employs a prospective, randomized, double-blind, placebo controlled study design to further demonstrate the safety and efficacy of VGX-3100 followed by EP in women with cervical HSIL associated with HPV-16/18. The primary clinical hypothesis is that VGX-3100 is a surgery-sparing, therapeutic option for the treatment of cervical HSIL and the underlying, pathogenic HPV-16/18 infection, which is supported by the findings of the Phase 2b trial. A placebo-controlled study is selected for this trial because it provides scientific rigor to distinguish an effective treatment, particularly in cervical HSIL for which spontaneous regression does occur.

1.2 DOSE AND REGIMEN RATIONALE

A total dose of 6 mg VGX-3100 DNA has been selected for this study based on previous human experience with both the WFI/LGS and SSC formulations of VGX-3100, preclinical data with VGX-3100 and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 3) without significant safety issues [19].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a true effect rather than random variation. Adverse events from previous human studies with VGX-3100 (frozen formulation) and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in the Phase 2b study. The results obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Table 3. Percent of Protocol HPV-001 Subjects Responding and Average SFU/10^6 PBMC in Responders for each Antigen by Cohort in Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	%Response	AVG	%Response	AVG	%Response	AVG
HPV-16E6	33%	107	50%	243	50%	1341
HPV-16E7	17%	198	50%	104	67%	143
HPV-18E6	50%	359	50%	338	83%	664
HPV-18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

1.3 RISKS/BENEFIT ASSESSMENT

1.3.1 RISKS ASSOCIATED WITH CURRENT THERAPEUTIC OPTIONS

Currently, treatment of women with cervical HSIL usually consists of either surgical removal of the affected tissue by CKC, LEEP, ablative therapy via laser, or cryotherapy. All treatments for cervical HSIL are associated with a variety of short and long term general and reproductive health risks as listed in Table 4.

Table 4. Risks Associated with Surgical Treatments for Cervical HSIL

Surgical Treatments for Cervical HSIL	Risks
CKC LEEP Ablative therapy (Laser or Cryotherapy)	Pain
	Exposure to anesthesia
	Heavy bleeding
	Infection
	Menstruation problems
	Cervical stenosis (can lead to alteration of squamo-columnar junction)
	Shortening of the cervix
	Decreased fertility/difficulty getting pregnant
	Cervical incompetence
	Pre-term birth and related low birth weight
	Incomplete treatment of cervical dysplasia
	Inadequate treatment of an occult early invasive cancer

Adapted from *FAQs Loop Electrosurgical Excision Procedure (LEEP) American College of Obstetricians and Gynecologists (2014) [11]*.

More importantly, none of the currently available surgical treatments for cervical HSIL eradicate the underlying cause of the high grade cervical dysplasia, persistent infection with one or more of the high-risk HPV types, and therefore, leaves patients at risk for recurrent cervical HSIL as well as high grade dysplasia of the vulva and vagina due to the potentially broader infection of the genitourinary area.

Although professional guidelines typically advocate immediate excisional therapy for adults with cervical HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [8]. The risk of a "missed diagnosis" of an occult early invasive cervical cancer exists for all current treatment modalities including surgical and ablative therapies. Furthermore, approximately 17-18% of patients with high grade CIN will experience recurrence of dysplasia following surgical intervention [8], which illustrates that current standard of care for cervical dysplasia requires improvement. The study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult early invasive cervical cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent cervical colposcopy, cytology and high-risk HPV testing throughout the trial. Investigators will be

comprised of experienced gynecologists, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

1.3.2 POTENTIAL RISKS OF STUDY PARTICIPATION

A risk associated with VGX-3100 for the treatment of high grade cervical dysplasia are the injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild (e.g. erythema) and limited to a few days in duration at most.

A second risk is the "delay" in "definitive treatment" of the high grade cervical dysplasia and the "missed diagnosis" of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not spontaneously regress. This risk is mitigated by careful serial cytology, HPV testing, and colposcopic exams, throughout the course of the study, and the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. Also, only investigators who are experienced in the management of cervical cancer will be chosen, and they will have the option of performing additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression.

A DSMB will also advise the Sponsor if it appears that the frequency of regression in the VGX-3100 group is unacceptably low compared to the placebo group. These measures should minimize the risk - even perhaps below that of standard care - of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. All subjects with suggestion of residual disease will undergo excisional therapy (e.g. CKC, LLETZ, LEEP) at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Tables 5 & 6) to provide histopathologic confirmation of regression. In the Phase 2b study, the rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

1.3.3 POTENTIAL BENEFITS OF STUDY PARTICIPATION

All currently accepted treatments for high grade cervical dysplasia are surgical procedures (LEEP, CKC, Laser ablation) which are all associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding and/or infection, damage to other organs, shortening and/or deformation of the cervix, pain, etc. Due to the risk of shortening and/or deformation of the cervix there are additional well accepted risks including cervical stenosis, infertility, cervical incompetence, preterm birth, and inability to visualize the transformation zone. Additionally, none of the surgical treatments systemically address the underlying oncogenic root cause, the high risk HPV infection in the lower genital tract, which leaves an underlying risk for further disease manifestations and transmission of HPV. VGX-3100+ EP is not associated with any of the risks associated with the surgical procedures outlined above (except for pain, which is transient and restricted to the deltoid/quadriceps treatment site) and has demonstrated the ability to not only eradicate the high grade dysplasia but also the ability to eradicate the underlying HPV infection.

Subjects receiving placebo, who represent women of child-bearing potential, may benefit from the opportunity to be closely managed under careful surveillance over the course of this study and those who regress spontaneously will be able to avoid excisional therapy.

2 STUDY DESIGN

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled study to determine the efficacy, safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18.

A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

Subjects will be randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category ($\leq$25 vs. >25 kg/m^2), and (c) age category (<25 years vs. $\geq$25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of cervical HSIL. Subjects must also have a cervical specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

2.1 ENDPOINT ASSESSMENT

In the Phase 2b study, subjects were randomized 3:1 to the VGX-3100 frozen formulation arm or the Placebo arm. All subjects were scheduled to receive treatment on Day 0, Week 4 and Week 12 and undergo repeat cervical biopsy or surgical excision (i.e. LEEP, LLETZ, CKC) of the cervix at Week 36 to assess efficacy. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit, and the secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less.

The primary endpoint for the Phase 3 study is based upon the results of the Phase 2b study. Given that HPV persistence is an important factor in the clinical progression of dysplasia and also based upon the findings of the secondary objective of the Phase 2b study, the responder definition for the Phase 3 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16/18.

The proportion of subjects who achieved this endpoint in the Phase 2b study was 35% (40%) of VGX-3100 subjects versus 14% (15%) for placebo, in an intention-to-treat analysis and modified intention-to-treat analysis, respectively. The composite endpoint of histologic regression and

virologic clearance will be primary in the Phase 3 study, and histologic regression endpoint will be a secondary endpoint.

2.1.1 HISTOLOGY ASSESSMENT

Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Digital photographs of acetowhite lesions are also used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression will be is obtained at Week 36 either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or by 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings as outlined in Tables 5 and 6 for subjects 25 years and above and below 25 years, respectively.

Table 5. Minimally Required Procedure at Week 36 for Subjects Age 25 Years and Above

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
25 and above	NA	NA	HSIL, ASC-H, AGC, Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	positive	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	negative	4Q biopsy and ECC
	unsatisfactory	no lesion	NILM	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Table 6. Minimally Required Procedure at Week 36 for Subjects Under 25 Years

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
18-24	NA	NA	Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	HSIL, ASC-H, AGC	NA	Tissue Excision
	unsatisfactory	no lesion	NILM, ASC-US, LSIL	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US, HSIL, ASC-H, AGC[b]	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

[b] if cytology result is AGC "favor neoplasia", tissue excision is recommended

2.1.2 VIROLOGIC (HPV) ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28, 36, 62, and 88. Also, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for testing of HPV-16/18. Vaginal and oropharyngeal samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 36, and 88 to assess virologic response to treatment at sites other than the cervix. Intra-anal samples will be

obtained (if subject consents to intra-anal sampling) to characterize HPV infection at Day 0 (prior to dosing) and at Week 36 to assess virologic response to treatment at sites other than the cervix.

2.1.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 7) for the primary endpoint takes into account both histopathologic regression of cervical HSIL and virologic (HPV-16 and/or HPV-18) clearance from cervical samples since HPV persistence is an important factor in the clinical progression of HSIL. The responder definition also excludes subjects whose cervix is biopsied at any time after their initial biopsy to determine eligibility and the Week 36 endpoint tissue collection. This exclusion is included to reduce the potential for artefactual increases in the treatment effect caused by removal of HSIL tissue and potentially HPV-16/-18 by unplanned interval biopsies. To qualify as a responder, the subject must have: 1) an acceptable histology specimen at Week 36, which is interpretable by the independent PAC, and 2) an acceptable HPV ThinPrep™ sample at Week 36, with an associated valid HPV-testing result. A responder is defined as a subject with: 1) no histologic evidence of cervical HSIL and 2) no evidence of HPV-16 or HPV-18 at the Week 36 evaluation. Also, to be considered a responder, the subject must not have had an unscheduled cervical tissue sample obtained after study entry and the Week 36 visit. Conversely, any subject with: 1) histologic evidence of cervical HSIL at the Week 36 evaluation, OR 2) evidence of HPV-16 or HPV-18 at the Week 36 visit, OR 3) a cervical tissue sample obtained after study entry and the Week 36 visit OR 4) no Week 36 visit sample will be designated as a non-responder.

Table 7. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 and/or HPV-18 at Week 36[b] AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit OR Subject with no Week 36 primary endpoint sample result

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

[b] the histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36

2.1.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100 treatment may be evaluated in blood samples taken at baseline (both screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Cervical tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Whenever possible, these studies may be performed on tissue sections from the diagnostic screening biopsy (pre-dose) and from tissue obtained post-dose(s) (Week 36).

2.2 TREATMENT PLAN

The three dose regimen of VGX-3100 appeared to be safe and well tolerated in the Phase 2b study, therefore all eligible subjects who consent to participate in the Phase 3 study will receive the same three 6 mg doses of VGX-3100 refrigerated formulation or placebo administered in 1 mL IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third (final) study treatment will be administered at Week 12 which is consistent with the Phase 2b study. The first study treatment will be given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16/18 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-16/18.

2.3 SAFETY MONITORING PLAN

Although cervical HSIL is thought to require years to progress to cervical cancer, subjects in the Phase 2b study were followed closely throughout. HPV testing (Weeks 14 and 24), cytology (Week 14) and colposcopy (Week 24) were all mandatory during the observation period prior to obtaining tissue for determination of the primary histologic endpoint at Week 36. Investigators were also instructed to perform additional testing (including biopsy) if disease progression was suspected. These instances were infrequent as only 11 unscheduled biopsies were deemed necessary over the course of the Phase 2b study. In addition, the rate at which occult microinvasive cancer was discovered after 36 weeks was less frequent than what is reported in the literature [22]. Both observations would imply that the mandatory monitoring employed in the Phase 2b study was sufficient; however cervical disease will be monitored even more closely in this Phase 3 study. Colposcopy, cytology and HPV testing will be required at 8 to 14 week intervals throughout the observation period leading up to the primary endpoint 36 weeks after the first dose. Although less frequent monitoring may be adequate, the more frequent monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy.

Safety monitoring will include:

- Local and systemic events for 7 days following each treatment as noted on a Participant Diary Card (PDC).
- All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

In the Phase 2b study, the safety profile was carefully evaluated and treatment with VGX-3100 was well-tolerated based on observations through Week 88 in all subjects. The most common adverse events were administration-site reactions, which included pain, tenderness, erythema and swelling, and were generally mild and limited to a few days in duration. Only erythema showed a statistically higher incidence in VGX-3100 (78%) vs. placebo (57%) in the 7- and 28-day periods after a dose. One additional AE, sinusitis, was also statistically significantly increased over the course of the entire study period but resolved without sequelae in the VGX-3100 arm compared to the Placebo arm (10% vs. 0%).

As outlined above, safety monitoring and visit frequency has been designed to take into account the potential risk of delay in the usual treatment of the high grade cervical dysplasia and also the potential for a missed diagnosis of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not regress. Serial cytology, HPV testing, and colposcopic exams are applied throughout the course of the study with the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. All subjects with suggestion of residual disease will undergo excisional therapy by LEEP or CKC at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Table 5 and 6) to provide histopathologic confirmation of regression. The use of a 4 quadrant biopsy in Phase 3 is a change from the approach used in Phase 2b to optimize the evaluation of histopathologic regression taking into consideration the inherent limitations of colposcopy and tissue biopsy samples in the absence of visible lesions [23].

In the Phase 2b study, the cervical tissue sample was initially read by a local pathologist and/or central pathology laboratory for rapid local medical management. The definitive histopathologic assessment was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US. Seven reports included the terms '(adeno)squamous cell carcinoma' or the premalignant condition of 'adenocarcinoma in situ' (AIS) in the final Phase 2b study results which included all 88 weeks of follow up. Three of the cases were reported as AIS, (2 VGX-3100, 1 placebo), out of which two cases (1 VGX-3100, 1 placebo) were confirmed as AIS by the Pathology Adjudication Panel. AIS is a pre-invasive glandular lesion which can be difficult to capture on standard of care screening with initial punch biopsy and is more commonly identified by full excision (e.g. LEEP, conization). There were four reports that included the term squamous cell carcinoma, of which two were confirmed by the Pathology Adjudication Panel, both in the VGX-3100 group. The other two cases (1 VGX-3100, 1 placebo) were diagnosed as CIN3 by the Pathology Adjudication Panel. The rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

Importantly, investigators in the Phase 3 study will be chosen only if they are experienced in the management of cervical cancer as was the case in the Phase 2b study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a

non-responder in the efficacy analysis as outlined in Table 6. These measures should minimize the risk of progression of cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. The frequency of close monitoring by experienced investigators should minimize the risk of cancer progression on the study what is expected with standard of care.

2.3.1 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will be scheduled to meet quarterly. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with regression in the VGX-3100 group is unacceptably low compared to the placebo group. However, no formal interim analysis will be performed.

2.4 LONG TERM FOLLOW UP PLAN

In the Phase 2b study, all subjects were scheduled to be followed for 1 year after the histopathologic assessment for the primary endpoint (to study Week 88). The establishment of efficacy based on histopathologic evidence dictated the removal of tissue at week 36 by either punch biopsy (ies) or more extensive surgical resection (i.e. LEEP, CKC). Subjects with colposcopic evidence of residual disease were to undergo LEEP/CKC. A higher proportion of patients who received placebo had a LEEP performed than those who received VGX-3100 (Table 8).

Cytology and HPV-16/18 clearance from the cervix was to be assessed at study Weeks 62 and 88 to evaluate for recurrence of dysplasia and HPV infection after removal of tissue at Week 36. Overall, in the phase 2b study, the majority of subjects had improved cytology and had cleared their underlying HPV-16/18 cervical infection by the Week 62 and 88 visits. For Weeks 62 and 88, there were no clinically meaningful differences noted between the subjects who received an excisional treatment (e.g. LEEP, CKC) and those that showed histopathologic regression and therefore only underwent a biopsy, as shown in Table 8 which summarizes the HPV and cytology results following Week 36.

Table 8. HPV-003 HPV and Cytology Results at Weeks 36, 62 and 88, mITT Population

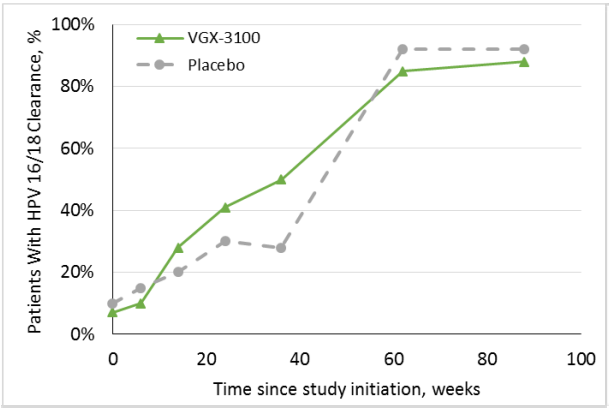
Week	Test[a]	VGX-3100		Placebo	
		LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	100% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89% (42/47)	89% (24/27)	100% (10/10)
88	Pap	96% (52/54)	91% (43/47)	85% (23/26)	100% (11/11)

Abbreviations: NA, not applicable, Pap smear was not done at Week 36
[a] HPV = HPV-16/18 testing; Pap = cytology testing
[b] LEEP or CKC done, at or before the study week as specified
[c] Only biopsy done, at or before the study week as specified

Clearance of HPV-16/18 from the cervix was observed in both treatment groups (Figure 1a) at similar rates until after the second dose when clearance in the VGX-3100 recipients continued to rise while the rate appeared to plateau in the placebo group.

Figure 1. HPV-16/18 Clearance and Pap Smear Findings in Phase 2b mITT Population by Treatment Group

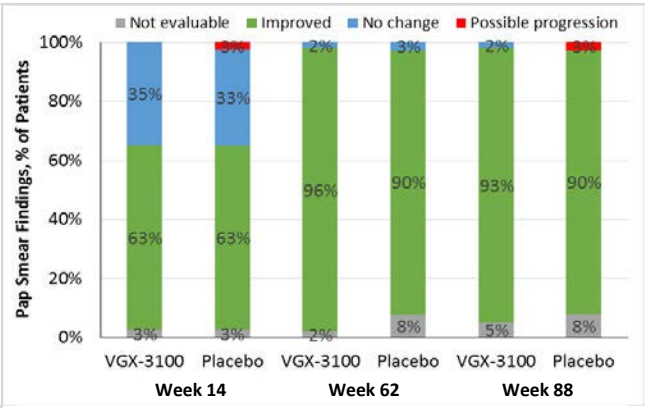
a.



No. of subjects

VGX-3100	123	62	118	116	115	108	103
Placebo	42	26	40	40	40	39	37

b.



No. of subjects

VGX-3100	118	108	103
Placebo	40	39	37

At Week 36, clearance was significantly higher among VGX-3100 subjects that had biopsy (63%) versus LEEP/CKC (41%), which likely reflects the association between clearance of the underlying HPV infection and the likelihood of having signs indicative of regression by colposcopic exam. HPV-16/18 clearance data (mITT population) post-Week 36 are described as follows: HPV-

16/18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% (42/51) for VGX-3100 post Biopsy only, 96% (27/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post Biopsy only. HPV-16/18 clearance at Week 88 was 89% (48/54) for VGX-3100 post-LEEP/CKC, 89% (42/47) for VGX-3100 post Biopsy only, 89% (24/27) for Placebo post-LEEP/CKC, and 100% (10/10) for Placebo post Biopsy only.

The majority of subjects had cleared their underlying cervical HPV-16/18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups. Forty-seven of 53 (89%) and 46 of 49 (94%) subjects at Weeks 62 and 88, respectively (mITT population) with histopathologic evidence of CIN2/3 regression (regressors) in the VGX-3100 treatment group experienced HPV-16/18 clearance. Despite the use of therapeutic resection for many VGX-3100 recipients whose CIN2/3 did not regress by Week 36 (non-regressors), HPV-16/18 clearance rates were notably lower (85% at Week 88) compared to regressors.

In the subjects who initially cleared HPV-16/18 by Week 36, only one HPV-16/18 recurrence was identified at the Week 62 and 88 evaluations. Specifically, one subject in the VGX-3100 group whose lesion was biopsied at Week 36 had HPV types 16 and 82 and CIN2 at screening, was HPV negative at Week 36, but tested HPV type 16 positive at Week 62, and then cleared HPV-16 at Week 88. The subject showed histopathologic regression at Week 36. No recurrences were identified in the eleven subjects in the placebo group whose lesions were biopsied at Week 36 with valid HPV data at Weeks 62 or 88. There were no (0/51) recurrences identified in the VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk as compared to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear cytology results at Week 62 were 93% (52/56) for VGX-3100 post-LEEP/CKC, 100% (51/51) for VGX-3100 post-Biopsy only, 93% (26/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post-Biopsy only. At Week 62, cytopathologic improvement was reported for 104 of 125 (83%) subjects in the VGX-3100 treatment group and 34 of 42 (83%) subjects in the placebo treatment group (mITT population).

There were no instances of possible progression, and all cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. Improvement compared to study entry for Pap smear cytology results at Week 88 were 96% (52/54) for VGX-3100 post-LEEP/CKC, 91% (43/47) for VGX-3100 post-Biopsy only, 85% (23/26) for Placebo post-LEEP/CKC, and 100% (11/11) for Placebo post-Biopsy only. At Week 88, possible progression (atypical glandular cells) was reported in a single Placebo subject in the post-LEEP/CKC group (3%) and no subjects treated with VGX-3100. All other cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. The majority of subjects showed improvement, and there was no meaningful difference between the Week 62 and Week 88 evaluations. These findings support that study subjects had no increased risk of progression based upon cytology as compared to standard of care.

The protocol-specified removal of dysplastic cervical tissue at Week 36 by either method substantially affected the clearance of HPV-16/18 and normalization of cytologic findings as expected, regardless of treatment group (Figure 1a, b). HPV-16/18 clearance rises at a sharp rate

after tissue is removed at Week 36 whether the excision is wide (e.g. LEEP, LLETZ, CKC) or more limited (biopsy). Notably, the method of tissue collection at the Week 36 endpoint did not appreciably affect the HPV-16/18 clearance rates beyond Week 36 (Table 8). Based upon the Phase 2b results, the risk of progression or recurrence of cervical dysplasia is low and comparable to the rates observed post-LEEP/CKC in clinical practice. The long term follow up planned for this Phase 3 study will include safety, cytology and HPV-16/18 testing at 6 months and also 1 year following the Week 36 histopathologic assessment, which is highly conservative given the expectation that few subjects will have persistent evidence of disease after the removal of tissue at Week 36 which is supported by the findings in the Phase 2b study.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 HYPOTHESIS

Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered IM followed by EP with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16/18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit.

3.2 PRIMARY OBJECTIVE AND ENDPOINT

Objective	**Endpoint**
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	Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit

3.3 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of SAE and UADE for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6.Determine the efficacy of VGX-3100 compared with placebo as measured by histopathologic non-progression	6. Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (i oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response following administration of VGX-3100 compared with placebo at post dose 3, Week 36 and Week 88 visits compared to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Week 15, 36, and 88 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, 36, and 88 visits 8c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.4 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Endpoints
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Evaluate effect of HLA type on efficacy	2. HLA (per-locus and per-allele basis) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Describe association of microRNA (miRNA) profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	3. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits) and miRNA profile (baseline, Week 8) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100 compared with those treated with placebo	4. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
5. Describe the patient-reported outcomes for subjects treated with VGX-3100	5. Patient-reported outcome questionnaires will be self-administered at baseline, Weeks 4, and 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK.

4 SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Women aged 18 years and above;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas^{TM} HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;

5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) WOCBP is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable:
        - Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
        - Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
        - Intrauterine device or intrauterine system
        - Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject
11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from enrollment in the study:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;

2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
3. History of ECC which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant during the study;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Cervarix™);
7. Presence of any abnormal clinical screening laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 or less than Grade 1 but deemed clinically significant by the investigator within 30 days prior to Day 0;
8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 30 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
9. Receipt of any non-study, non-live vaccine within 2 weeks of Day 0;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
12. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;

14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests Grade 3 toxicity attributable to the study treatment, the medical monitor and Investigator will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All randomized subjects should be encouraged to complete all study treatments and follow-up visits. A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule for follow-up and treatment of HSIL (CIN2, CIN3), and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/ WITHDRAWAL

The investigator or study coordinator must notify the Sponsor within 24 hours if a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1 – Safety Parameters.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the CRF:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death of subject
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the CRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a medical need to withdraw the subject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject from participation in the study
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including telephone calls, letter sent by certified mail or equivalent.
- Other: The subject was terminated for a reason other than those listed above, such as the termination of the study by the Sponsor.

4.3.5 SUPPLEMENTATION OF STUDY SUBJECTS

If more than 10% of subjects from randomization of study treatment discontinue prior to the Week 36 primary endpoint procedures, then supplementation of study subjects will be considered.

5 STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The active and placebo formulations to be used in this study are described in Table 9. Both IPs will presented in clear glass cartridges and will be injected intramuscularly.

VGX-3100 and placebo will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 9. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Placebo	150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 BLINDING

This study is double-blinded with blinding maintained throughout the study by use of identical packaging for both the active product and the placebo. There is no difference in appearance for both the active product and the placebo.

The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is essential for proper clinical management of the subject, as judged by the investigator. It is preferred, but not required, that the investigator first contact the Medical Monitor to discuss options before unblinding the subject's treatment assignment. In case of non-emergency, investigator must contact Medical Monitor to discuss the options before unblinding the subject's treatment assignment.

The Sponsor's or designee's pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE, UADE, or AE of interest. No personnel directly involved with the study will be unblinded. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's treatment assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCT

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, double-panel label with tear-off. Both VGX-3100 and placebo labels will include, at minimum, the following information in Table 10:

Table 10. Example Labels for Investigational Product

Cartridges (primary container)	**Pouches** (secondary package)
VGX-3100 or Placebo Insert cap end IM administration Inovio Pharmaceuticals, Inc.	Study ID/Material ID VGX-3100 or Placebo Single-use, 1 mL Storage temperature, expiration date CAUTION: New Drug – Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.4 HANDLING OF INVESTIGATIONAL PRODUCT

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Unless otherwise specified, IP will be shipped in a refrigerated condition

with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Immediately upon arrival, IPs should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition.

Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

5.5 DISPENSING OF INVESTIGATIONAL PRODUCT

It is the responsibility of the Investigator to ensure that the IP is only dispensed to study subjects. It must be dispensed only from official study sites by authorized personnel according to local regulations.

When a subject is eligible for randomization, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration. The pouch must not be discarded until 1) administration is completed and 2) all pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator.

The device user manual and instructions for use will inform clinical personnel about placement of the IP cartridge into the device, as well as the steps for injection and electroporation.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at site per institution policy or returned to Inovio Pharmaceuticals, Inc. or its designee, if site cannot destroy IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor.

The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

If IP is returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

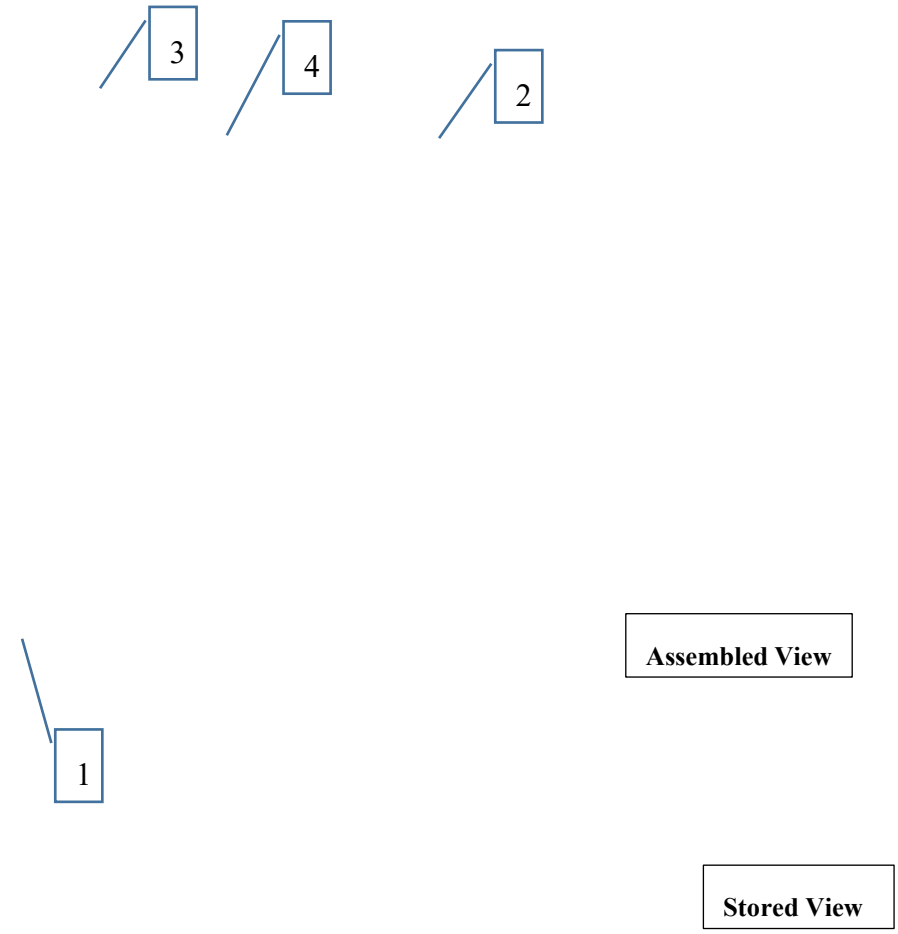
5.8 INVESTIGATIONAL DEVICE

The needle array component of CELLECTRA™ 5PSP device is provided sterile and is intended for single-use. CELLECTRA™ 5PSP device is intended to be used by qualified and trained healthcare professionals in clinical settings. The Investigator for this study will be trained in the use of the device.

CELLECTRA™ 5PSP has 3 main components that are used in conjunction with the drug cartridge (see Figure 2):

1. **Base** – Acts as a docking station for the Handset and as the primary display for entering subject information; must be used with the provided Power Supply
2. **Handset** – Controls delivery of the drug and electrical pulses
3. **Array** (single-use sterile) – Attaches to the Handset and contains the injection needle, electrodes and sensors used for drug delivery and electroporation.
4. **Drug Cartridge** (single-use) – a separate container-closure containing the IP solution. The Cartridge is inserted into the array for administration of the IP.

Figure 2. Components of the CELLECTRA™ 5PSP Device and Drug Cartridge



The CELLECTRA™ 5PSP device has unique features that make using it different from using other injection systems:

1. Each Handset is uniquely paired to a Base. The serial numbers on the bottom of the Base and Handset must match.
2. There is no communication between the Base and Handset when separated; the Handset must be placed onto the Base to share power or data.
3. The Handset has an internal battery that must be charged on the Base before use.
4. Needle depth is selectable on the Handset at the following lengths: 13 mm, 19 mm, or 25 mm. Even though the system provides a needle depth recommendation based on a Subject's height and weight, the user will be asked to manually enter the needle depth based on the protocol requirements (refer section 5.9), described
5. Injecting the placebo and delivering electrical pulses takes time (usually 10 seconds). The Handset will let you know when treatment is complete.
6. The Subject should be maintained in a safe and secure, braced position due to involuntary muscle spasms that may occur during delivery of the electrical pulses.

Before using the CELLECTRA™ 5PSP device, the Investigator and research staff must be trained by the Inovio Pharmaceuticals Inc. device trainer(s) and be requested to read the entire user manual and complete the Self-Assessment.

5.9 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the device are located in the CELLECTRA™ 5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training. Training will include review of the entire device user manual and instruction video and hands-on training. After training on the proper use of the CELLECTRA™ 5PSP device, intended users at each site will be required to demonstrate their competence in its use to Inovio or its designee.

Briefly, the Handset and Array should be prepared according to the instructions in the user manual. Remove the array from its packaging while avoiding contact with the end of the array that attaches to the handset, and insert the drug cartridge into the array with the arrow on the cartridge pointing away from the handset.

Attach the Array to the Handset and set the needle depth on the handset to the longest needle length judged to allow safe injection into the muscle per the investigator's assessment.

The subject must be in a safe and secure, braced position. The subject's body should touch the bed or be braced against the bed or have the study staff performing electroporation or assistant in position to brace the subject's arm or leg (as appropriate) as the EP is administered. The user will then insert the CELLECTRA™ 5PSP needle array into the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) of the subject in accordance with the CELLECTRA™ 5PSP user's manual instructions. Once triggered by the user, the device will automatically deliver the blinded treatment followed by the EP pulses. The entire treatment period lasts for about 10 seconds.

The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel. Individuals whose credentials do not meet the relevant local requirements may perform the treatment procedure under both of the conditions below:

1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform the procedure.

Any deviation from the above procedures must be approved by the sponsor or its designee.

5.10 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

See below Figure 3 for example CELLECTRA™ 5PSP device component labels.

Figure 3. Device Labels (Base, Handset, Array)

BASE **HANDSET**

ARRAY

5.11 HANDLING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual.

5.12 INVESTIGATIONAL DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining investigational device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational product. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP serial number, array lot number and the study drug lot number. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.13 RETURN OF INVESTIGATIONAL DEVICES

Upon completion or termination of the study, all investigational devices and unused components must be returned to Inovio Pharmaceuticals, Inc.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by the responsible Study Monitor.

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions will not be granted with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct.

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who have been identified with standard of care biopsy results of CIN 1/2, CIN 2, CIN 2/3 or CIN 3 and who consent to participate in the study will be eligible for screening and will have biopsy slides or tissue sent to the central pathology lab for review by PAC for evaluation prior to enrollment.

Additionally, Investigators may discuss with the Sponsor on a case-by-case basis the screening of subjects with abnormal cytology findings (e.g. HSIL or ASCUS with or without local HPV-16 or 18 genotype results) obtained as part of standard of care. The specific circumstances MUST be submitted in writing (e.g. email or fax) and the medical monitor MUST be consulted prior to screening a volunteer with these cytology findings (e.g. ASCUS or HSIL with or without HPV-16 or 18) for this study. The initial biopsy results may have been obtained at a referring institution by someone other than the site investigator.

- In the case where the subject has an ASCUS or HSIL cytology result without HPV-16 or 18 genotyping results available locally and if approved by Inovio, the site may proceed with initial study screening by sending ThinPrep™ samples to the central laboratory to screen for HPV 16/18 by cobas™ assay. A non-specific result from local testing of "Positive for high risk HPV" is not sufficient and will require the collection of the ThinPrep™ sample for HPV-16 and/or HPV-18 testing by cobas™ assay. If the central lab ThinPrep™ sample result is positive for HPV-16 and/or HPV-18, the site may continue screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.

- In the case where the subject has an ASCUS or HSIL cytology result with HPV-16 or 18 positive genotype results available locally and if approved by Inovio, the site may proceed with initial study screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.

Subjects who consent to participate will have biopsy slides or paraffin-embedded tissue block(s) from a previous biopsy and/or newly collected cervical biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by PAC. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

- Biopsy specimens and colposcopic photographs obtained within 10 weeks prior to Day 0 as part of standard of care before the informed consent may be used as part of the screening and evaluation process. If the pathology results of the initial biopsy obtained as part of standard of care are available confirming the presence of cervical HSIL (CIN2 or CIN3), those biopsy slides or sample(s) may be sent directly to the central pathology lab after the subject has signed the informed consent.
- For those individuals diagnosed with cervical HSIL by a local pathologist, where the initial biopsy slides or tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, colposcopy with cervical photography may be performed and an additional biopsy sample may be collected during screening at the discretion of the investigator and consent of the subject. The 10 week screening window begins upon collection of the biopsy sample that will be evaluated by the PAC.

Subjects must have a histologic diagnosis of cervical HSIL (CIN2 or CIN3) confirmed by the PAC and a screening ThinPrep™ cervical specimen test positive for HPV-16 and/or HPV-18 by cobas™ HPV test to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18. The assessments during the screening period will determine the subjects' continued eligibility for the study and also their ability to comply with protocol requirements by completing all assessments.

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the safety laboratory collections/assessments, which must be performed within 30 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent
- Demographics; including age, and race/ethnicity
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- Full Physical Examination (including height, weight and BMI measurements)

- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Urine pregnancy test
- Colposcopy with lesion photography and/or cervical biopsy
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 30 days prior to Day 0);
- Serology (HIV Antibody, within 30 days of Day 0)
- Determination of eligibility per inclusion / exclusion criteria
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluations will be performed on **Day 0 prior to study treatment:**

- Determination of eligibility per inclusion / exclusion criteria
- Randomization
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile (a total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0)
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Oropharynx (OP) sample by oral rinse and vaginal swabs for HPV testing
- Intra-anal swabs (if subject has consented for intra-anal sampling) for HPV testing
- Colposcopy with lesion photography
- Patient-Reported Outcome (PRO) questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

Study treatment will be administered and the following evaluations will be performed on **Day 0 post-treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment

- Distribute Participant Diary Card (PDC)
- Download EP data from device within 24-48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review Day 0 PDC (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.3 WEEK 4

The following study evaluation will be performed on **Week 4 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect PDC for dose 1

The following study evaluations will be performed **on Week 4 post treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 24-48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.5 WEEK 8

The following study evaluation will be performed during the visit

- Vital sign
- Targeted Physical assessment
- Collect and review PDC for dose 2
- Post treatment adverse event and injection site reaction evaluation
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Whole blood and serum for immunology including miRNA profile

6.2.6 WEEK 12

The following study evaluation will be performed on **Week 12 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test

The following study evaluations will be performed **Week 12 post treatment**:

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 24-48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.7 8-14 DAYS POST DOSE 3 PHONE CALL

The following information will be evaluated during phonecall:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 3 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.8 WEEK 15

The following study evaluations will be performed on **Week 15 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Post-treatment injection site reaction assessment
- Urine pregnancy test

- Whole blood (at least 51 mL) and serum (at least 4 mL) for immunology
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Collect PDC
- Colposcopy and lesion photography

6.2.9 WEEK 28

The following study evaluations/actions will be performed on **Week 28 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Colposcopy and lesion photography to assess for possible disease progression
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 28 visit by a subject enrolled in US, Canada, Mexico, Germany and UK only

6.2.10 WEEK 36

The following study evaluations will be performed on **Week 36 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Socio-Behavioral assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Whole blood and serum for immunology
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Oropharynx (OP) by oral rinse and vaginal swab for HPV testing
- Intra-anal swab (if subject has consented to intra-anal sampling) for HPV testing
- Colposcopy and lesion photography
- Biopsy or surgical excision based on information collected at Week 28 to determine the minimally required tissue collection procedure (e.g. 4 quadrant biopsies, 4 quadrant biopsies and ECC, or surgical excision) to be used for histopathologic assessment at Week 36 as described in Tables 5 & 6

- PRO questionnaire (EQ-5D-5L only) completion by a subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.11 WEEK 40 PHONE CALL

The following study evaluations will be performed on **Week 40 ± 2 weeks** via a phone call:

- Review of histology results as read by PAC from Week 36
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 40 by a subject by subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.12 WEEK 62

The following study evaluations will be performed on **Week 62 ± 2 weeks:**

- Targeted physical assessment
- Vital Signs
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy and lesion photography

6.2.13 WEEK 88

The following study evaluations will be performed on **Week 88 ± 2 weeks:**

- Full Physical Exam
- Vital Signs
- Socio-Behavioral Assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- 2 Digene cervical swab samples
- Oropharynx (OP) by oral rinse and vaginal swabs for HPV testing
- Colposcopy and lesion photography
- Whole blood and serum for immunology
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with [redacted] (e.g., [redacted]). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.3 SAFETY EVALUATIONS

6.3.3.1 Physical Exam

A full physical examination (PE) will be conducted during screening and study discharge. It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

A targeted physical assessment will be performed at other visits as determined by the investigator or directed per subject complaints.

6.3.3.2 Vital Signs

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 Weight and Height

Weight and height will be collected at screening in order to calculate the BMI. Weight will be collected on Day 0, Weeks 4 and 12.

6.3.3.4 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. The medical history will include a) any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s), and b) if treated previously for CIN, the respective treatment type(s) and date(s).

6.3.3.5 Socio-Behavioral Assessment

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 36 and 88, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 Laboratory Evaluations

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- Serum glutamic-pyruvic transaminase (SGPT)/Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose $\geq$ 1+) a microscopic examination should be performed.

6.3.3.7 Demographics

Demographic information will be collected via self-report (unless noted otherwise), including the following:

- Age
- Race/ethnicity

6.3.3.8 Urine Pregnancy Testing

For subjects of reproductive potential, a negative spot urine pregnancy test is required prior to each study treatment, colposcopy and surgical excision.

6.3.3.9 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QTcb or QTcf, ST segment, T wave as well as an investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as "clinically significant (CS)" or "not clinically significant (NCS)" by the investigator.

6.3.3.10 Subject Self Evaluation

Subjects will be provided a PDC (as shown in Appendix A) and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PDC will be reviewed with the subject by the study staff at 8 -14 dDays post-dose phone call and next in-person visit.

The study staff will review the PDC for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse event accordingly in CRF.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a 3-dose series of either 1 ml VGX-3100 or Placebo by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with the CELLECTRA™ 5PSP. Study treatment must not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.4.1 RISKS OF TREATMENT PROCEDURES

Table 11 summarizes reported AEs and potential risk to study treatment.

Table 11. Summary of Reported Adverse Events and Potential Risks or VGX-3100 Delivered IM EP with CELLECTRA™ 5PSP

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration
Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury[1] • Disruption of function of implanted electronic medical devices (if CELLECTRA™ 5PSP device is not used per User Manual)[1] • Exacerbation of unstable cardiac disease[1] • Effects on the fetus and on pregnancy

[1]device only

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO TREATMENT

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

Medication taken for anxiety or pain management should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening will be performed for inclusion into the study as listed in section 6.1.1.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and within minimum of 30 minutes after each study treatment and at 2 to 4 weeks post study treatment visits. They will also be advised to record local and systemic AEs for 7 days on a PDC as shown in Appendix A.

A Medical/Clinical Assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 12. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, two previously-validated patient-reported outcomes (PRO) instruments will be provided to the subjects enrolled in US, Canada, Mexico, UK and Germany. The following two PRO questionnaires will be used:

1. Short Form Health Survey, **version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [24]
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [25, 26]

Either one or both PRO instruments (refer to Section 6.2) will be provided to the subject who will be instructed to complete the questionnaire at the following time points:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- Week 4 (after study treatment)
- 8-14 days post dose 2
- Week 12 (after study treatment)
- 8-14 days post dose 3
- 8 -14 days post Week 28
- Week 36 (after biopsy or surgical excision)
- 8-14 days post Week 40
- Week 88

Administration of PRO instruments will be performed according to the validated procedure and guidelines of each respective instrument, except for some assessments for exploratory analyses. Additional instructions will be provided separately

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 8, 15, 36, 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine 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). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 as well as Week 8. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 8 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 HLA TYPING

HLA testing will be performed on PBMC from any single blood sample collected for immunogenicity analysis. If the subject has a record of previous high resolution HLA testing and access to the results, then HLA testing is not required.

The DNA extracted from the blood sample will be used to determine if alleles at the MHC locus affect the immune response to study treatment. Data arising from this analysis will be subject to the same confidentiality restrictions as the rest of the study. This specimens will be destroyed after the analysis is completed.

6.12 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at the screening, Day 0, Weeks 8, 15, 28, 36, 62, 88 and read in a central laboratory. HPV PCR by cobas™ HPV test will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer at Day 0, Weeks 15, 28 or 36, the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples to eliminate potential interference with the results of HPV testing.

At visits (i.e. Screening, Day 0, and Weeks 15, 28, 36 and 88) where multiple cervical samples are collected, the two Digene cervical swab will be collected prior to the ThinPrep™ sample. Immunology testing may be performed from digene swab.

Details of sample collection and shipment information will be provided in laboratory manual.

Additionally, if there is residual tissue available from cervical tissue from screening and Week 36 after the histologic diagnosis have been rendered, then unstained slides and/or paraffin blocks may be collected to test for HPV typing.

Also, non-cervical swabs (i.e. oropharyngeal rinse, vaginal brush and intra-anal swabs) will be collected at specified visits for HPV typing.

6.13 COLPOSCOPY AND CERVICAL BIOPSIES

Colposcopy at screening must be adequate, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected dysplasia. An ECC is not required for study entry. However, if an ECC was done as part of routine care during the screening period, and found to have evidence of cervical HSIL such subject should not be enrolled in the study. Colposcopy is not required to be performed at screening if adequate colposcopy was previously obtained upon collection of initial biopsy. All colposcopies performed after informed consent should be conducted according to the guidelines outlined in Appendix B.

Interval colposcopies will be performed at Day 0, Weeks 15, 28, 36, 62, and 88. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

Digital photographs of the cervix will be captured after application of acetic acid at each colposcopic examination to document the clinical findings. If a biopsy or surgical excision is performed, images of the cervix should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach and 2) the process for uploading the images to a secure server. Additionally, if a vaginal or vulvar lesion should develop after a subject is enrolled, photographs should also be taken to document the clinical exam finding.

6.13.1 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at screening to confirm eligibility. If the criteria outlined in Table 5 or 6 are met, ectocervical biopsies may also be performed at Week 36 to provide tissue for histopathologic assessment of disease regression.

Visualization of a normal appearing cervix by colposcopy is insufficient evidence to confirm disease regression at Week 36. Biopsy must be performed at the location of the screening biopsy if no disease is visible at Week 36.

Biopsies should not be performed at any other visit unless there is suspicion of disease progression. Removal of additional tissue by biopsy before Week 36 will bias results toward improvement regardless of whether the subject is in the active or placebo group. The bias introduced will obviously be more significant for smaller lesions. For this reason, if biopsies are obtained prior to Week 36, the subject will be classified as a non-regressor in the efficacy

analyses. Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy prior to Week 36, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.13.2 UNSCHEDULED BIOPSIES

In the event an unscheduled biopsy is performed prior to Week 36, the subject will be classified as a non-responder. The subject will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and the Investigator's judgement based on the results of the histological diagnosis from the unscheduled biopsy Additional instructions for collecting ectocervical biopsies are detailed in Appendix B. All biopsy samples/excised tissue will be sent to the central pathology lab for review by PAC.

6.14 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to the screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.15 RESTRICTIONS

6.15.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled otic and ophthalmic corticosteroids are allowed
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine
- Blood thinners (e.g. anticoagulants, antiplatelet drugs) or other medication that affects blood clotting within 2 to 14 days (e.g., 4-5 drug half-lives) of any study treatment, biopsy or excisional procedure (e.g. LEEP)

6.15.2 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal death, still birth, congenital anomaly of the fetus/newborn); see Section 7.1.9 for additional information on pregnancy reporting.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.

- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.2.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.
Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.2.2 Event Reporting for Disease Progression or Exclusionary Histologic Findings Post-study Treatment

After starting study treatment, if there is histologic confirmation of progression of cervical HSIL to micro invasive or invasive squamous cell carcinoma, the event must be reported as an SAE. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances, the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.3 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification

of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.4 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

For countries recognizing and regulating CE Mark devices, SAEs related only to the device which meet the medical device vigilance (MDV) reporting criteria will be handled by the Sponsor under the post-market surveillance/vigilance reporting requirements per MEDDEV 2.12-1. In such cases, the Sponsor will report as per the regulations to the relevant health authorities that require MDV reporting.

7.1.5 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported.

The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)

The investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.6 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the investigational device. An AE may also be assessed as not related to the IP and/or the investigational device. Because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE.

The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the investigational device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event.

7.1.7 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

7.1.8 POST-STUDY REPORTING REQUIREMENTS

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.9 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to Week 36 will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor or its designee within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax, as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF THE COLLECTION AND RECORDING OF SAFETY DATA

Non-serious AEs and SAEs (and UADEs) will be collected for each subject from the time when informed consent is obtained through Week 88.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE (or UADE) occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100/placebo delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

- Grade 3 or greater persistent administration site erythema, and/or induration recorded ≥ 2 hours immediately after Study Treatment
- Grade 4 or greater persistent administration site pain, tenderness recorded ≥ 2 hours immediately after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

Sites will inform the Sponsor via method described in section 7.4.1 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

- If at any time during a study one-third (1/3) or more of the subjects experience an AESI, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB. Only the DSMB may review unblinded data in making their recommendation to the Sponsor regarding continuation of a trial.

- If any SAE (or potentially life-threatening AE), or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

- If three or more subjects in this study, experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

The sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

7.4 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the AE CRF.

7.4.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) (see Section 7.3.1) require expedited communication from the Site to the Sponsor. Within 24 hours of the site's awareness of the event, AESI must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the investigator must notify the Sponsor via email or phone.

AESI reporting if EDC system is unavailable

EMAIL: [redacted]
SAFETY PHONE: [redacted]

7.4.2 STUDY REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol. An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.3 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.4 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy. At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to the Sponsor or the appropriate designee.

Within 24 hours of the site's awareness of the event, all SAEs (regardless of relationship to investigational product) must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the paper SAE Report form should be used and faxed to the PPD Pharmacovigilance (PVG) Safety Hotline Fax Number shown below:

Facsimile (FAX) reporting if required[a]:

Americas FAX#: [redacted]
Europe FAX#: [redacted]

a: Reporting by FAX is required for paper SAE Report Forms if electronic data capture (EDC) is not available, redacted supporting medical records, and Pregnancy Report Forms.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor. The supporting documents for SAE reports should be sent by fax to the PPD PVG Safety Hotline Fax Number, shown above.

Investigator will supply the Sponsor and the IRB with more information as it becomes available and any additional requested information. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.3 and 7.1.4).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to

the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor with 10 days of discovery. Any product complaint that involves an AE or SAE must be also reported per Section 7.4.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation.

Additional instructions on reporting to be provided separately.

7.5 STUDY DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8 STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects with a histologic diagnosis of cervical HSIL. The study's primary endpoint is binary: regression to CIN1/normal and clearance of HPV-16 and/or HPV-18 infection, based on tissue collected at Week 36. The primary hypothesis is that VGX-3100 will be superior to placebo regarding the proportion who achieve the primary endpoint. Secondary efficacy analyses involve regression to CIN1/normal, clearance of HPV-16 and/or HPV-18 infection from cervical tissue and non-progression of cervical lesions. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, and virology and efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized (2 VGX-3100:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) BMI category ($\leq$25 vs. >25 kg/m^2), and c) age category (<25 years vs. $\geq$25 years). There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The study is double-blinded.

8.3 SAMPLE SIZE/POWER

A sample of 198 subjects will be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 35% and 14% for VGX-3100 and placebo, respectively. These proportions also incorporate missing data (~10%) classified as non-regressors (failures). The assumptions are based on the Phase 2 study results.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The intention to treat (ITT) population includes all subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be primary for the analysis of efficacy in this study.
- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding ITT population for the analysis of efficacy.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding ITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true population probabilities of the primary endpoint for VGX-3100 and Placebo, respectively. The primary hypothesis of superiority is:

$$H_0: \delta \leq 0 \textit{ vs. } H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [27]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

The secondary efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. It also includes subjects who undergo early intervention prior to this time frame or subjects who have no endpoint data for this time frame; these subjects are considered as failures for the efficacy endpoints. Table 13 provides details for the definition of the primary endpoint response.

Table 13. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 and/or HPV-18 at Week 36[b] AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit OR Subjects with no Week 36 primary endpoint visit sample result

[a] no evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL
[b] the histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36

Exploratory analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) colposcopy results, d) cytology results, and e) HPV results. As each of these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

Other exploratory analyses will examine durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue at Weeks 62 and 88. Descriptive statistics will be utilized; percentages of subjects who cleared will be presented by time point or anatomic location and treatment group.

8.10 IMMUNOGENICITY ANALYSES

Post-baseline cellular and humoral response magnitude may be compared between treatment groups using a difference in medians and associated non-parametric 95% CI. Post-baseline tissue response magnitude will be compared between treatment groups using a difference in means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

The mITT population will be used for immunogenicity analyses.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system

organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [27]. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

Any AEs with a missing or partial onset date will be included in the overall AEs, but not be included within specified day-range summaries. AE duration will be calculated as (Stop Date – Start Date) + 1.

8.11.2 LABORATORY DATA

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

8.12 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

8.13 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the ITT population.

8.14 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes among subjects who receive VGX-3100 will be compared between those with excision versus those without excision, based on PRO endpoints. This comparison will utilize the median difference in endpoints or the difference in proportions of subjects with endpoints and associated non-parametric or Miettinen and Nurminen [27] 95% CIs, for continuous responses and binary responses, respectively.

The mITT population will be used for PRO analyses.

8.15 MISSING VALUES

Missing data will be considered as non-regressors (failures) for the ITT efficacy analysis. A subject's regression outcome is missing if her CIN grade and HPV clearance at Week 36 cannot be determined. Also, any subject who undergoes an unscheduled procedure in which cervical tissue

sample was obtained before Week 36 will be considered a non-regressor regardless of the Week 36 result.

Efficacy analyses using the mITT population will be conducted and will serve as sensitivity analyses regarding missing data.

8.16 SUBGROUP ANALYSES

Primary and secondary efficacy endpoints will be analyzed by history of exposure to prophylactic HPV vaccines.

8.17 INTERIM ANALYSIS

No formal interim analyses will be performed for this study. For reasons of futility (early evidence of poor efficacy of VGX-3100) or safety issues, the DSMB could recommend stopping enrollment at any time. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

9 DATA COLLECTION, MONITORING AND REPORTING

9.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

9.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. This retention period may be superseded by applicable regulatory requirements (e.g. minimum of 25 years for Health Canada). The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.4 SAFETY AND QUALITY MONITORING

9.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The DSMB charter will define the membership, responsibilities and procedures for the meeting.

9.4.2 PATHOLOGY ADJUCATION COMMITTEE

All histology slides (i.e. cervical biopsies or surgical excision tissue) will be read by a Pathology Adjudication Committee (PAC) to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion. If the two pathologists agree the reading will be considered the clinical disease status for the subject. If the readings of the first two pathologists are discordant, the third pathologist will review the discordant slide(s) independently and if there is agreement among any of the three readings, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the most severe diagnosis would be deemed the final diagnosis.

9.4.3 CLINICAL MONITORING

Clinical Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
    - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
    - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Assure that the study facilities continue to be acceptable
    - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

10 ETHICS

10.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2 INSTITUTIONAL REVIEW BOARD OR INSTITUTIONAL ETHICS COMMITTEE (IRB/IEC)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/IEC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/IEC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/IEC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

10.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

11 PROTECTION OF HUMAN SUBJECTS

11.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

11.2 COMPLIANCE WITH IRB/IEC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator must be provided to Sponsor.

11.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

11.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

11.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Product used in this study however will be asked to complete a participant diary card during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

11.6 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the sponsor in all participating countries and is fully supporting the study. Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted.

13 PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

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15 APPENDICES

15.1 APPENDIX A: PARTICIPANT DIARY CARD

Subject Diary

HPV-301

Subject #: _____

Injection Date:_____

Note to Participant:

For questions or problems, please contact your Site Coordinator.

Name: _____

Telephone: (_____) _____

Email (optional): _____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

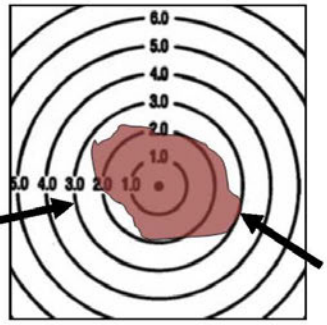
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 0: Evening of Injection Subject #: _____ Date: _____/_____/_____

Sometime during the evening on the day you were injected, fill out the information below. The items on this page refer to the time from your injection to 11:59 p.m. on the day of injection (Day 0). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst the symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 2.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

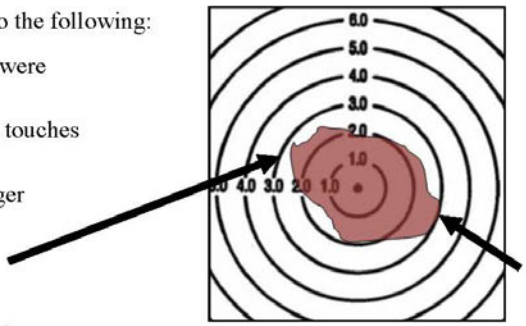
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 1: 1 Day After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 1). If any of the information changes after you fill out this page but before 11:59 p.m. tonight make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 4.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

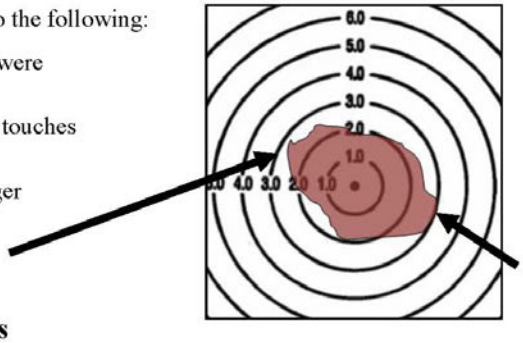
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 2: 2 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 2). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describesyour worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 6.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

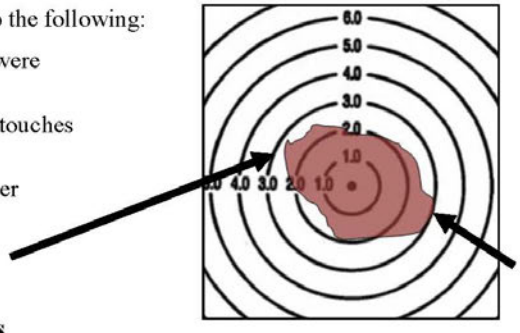
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 3: 3 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 3). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m.tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 8.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

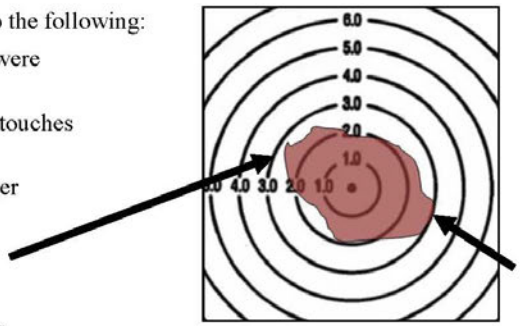
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 4: 4 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 4). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 10.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

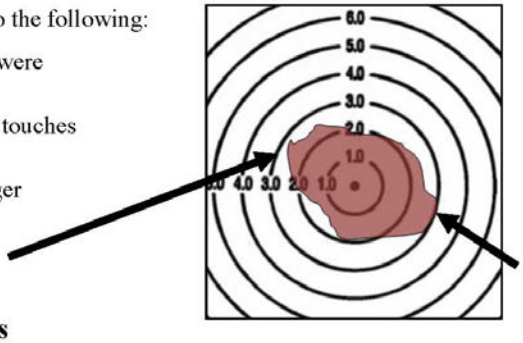
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 5: 5 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 5). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 12.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

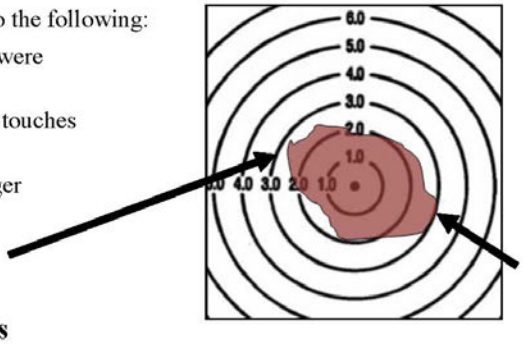
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 6: 6 Days After Injection Subject #: _____ Date: _____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 6). If any of the symptoms you reported on previous pages have not gone away ("resolved"), you will need to let the Site Coordinator or Doctor know.

Temperature

Evening Temp.: _____ °C or °F (circle one)	Time Taken: _____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	____ cm at the longest part
Swelling	☐	____ cm at the longest part
Bruising	☐	____ cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 14.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

15.2 APPENDIX B: GUIDELINES FOR COLPOSCOPY, BIOPSY, AND SURGICAL EXCISION

Colposcopy Procedure

It is recommended that all study colposcopies performed after informed consent be according the procedures recommended by the American Society of Colposcopy and Cervical Pathology (ASCCP):

1. Use warm, clean water to lubricate the vaginal speculum. Avoid other lubricant substances which could obscure results.
2. If the vaginal walls are lax, a lateral vaginal sidewall retractor aligned perpendicular to the speculum may facilitate visualization.
3. Examine the cervico-vaginal secretions and remove any excess mucus from the cervix with saline-soaked cotton swabs.
4. Obtain any required specimens required for cytology and HPV testing.
5. Using low-power magnification (5x to 10 x) inspect the cervix for obvious areas of abnormalities.
6. Swab or spray the cervix with 3-5% acetic acid. Reapply every 2-3 minutes during the examination.
7. Use the green or blue filter to examine blood vessels. Increase magnification (15x)
8. Identify the distal and proximal boarders of the transformation zone.
    a. The inner border is the entire 360-degree circumference of the squamocolumnar junction
        i. If the junction is proximal to the external os, in the canal, use a cotton-tipped applicator to pry either the anterior lip up or the posterior lip down or use an endocervical speculum
        ii. If the junction is not visualized in its entire circumference, the colposcopy is deemed inadequate
    b. The distal limit of the transformation zone may be identified by finding the most distal crypt openings or nabothian follicles in the lips of the cervix and drawing an imaginary line connecting these landmarks
9. Inspect the entire new squamocolumnar junction and detect and evaluate any abnormal areas.
10. Evaluate the upper third portion of the vagina.
11. Lugol or Schiller's solution may be applied to further define previously identified lesions.

Cervical Biopsies

Endocervical Curettage

ECC is to be performed using a kervorkian curette or equivalent instrument. Rotate and scrape the curette 360° in the endocervical canal and use a cytobrush to remove the specimen. Deposit the specimen onto a Telfa pad before depositing in the specimen vial containing 10% neutral buffered formalin solution and labeled with the subject identification (SID) number.

Ectocervical Biopsies

Ectocervical biopsies should only be performed prior to Week 36 if disease progression is suspected. Only the suspect lesion should be biopsied in that circumstance.

If the subject is eligible for 4 quadrant biopsy at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the subject's ID number and the quadrant number according to the figure below.
2. Perform and record colposcopy findings from each quadrant according to the following categories

a. Negative (no lesion present)
b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
d. Suspicion of invasive cancer
e. Invasive cancer

3. Perform colposcopic directed biopsies from all quadrants with lesions.
4. Multiple biopsies can be obtained of a lesion at the discretion of the investigator but must be uniquely labeled
5. If a quadrant is free of lesions, obtain a random biopsy at the squamocolumnar junction in that quadrant at 2, 4, 8, or 10 o'clock.
6. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Figure 1 – Biopsy Quadrant Numbers

Surgical Excision

For subjects undergoing surgical excision at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the SID number and the specimen type.
2. Record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform the LEEP or CKC per usual practice.
4. Specimen should be marked at 12 o'clock with suture or gentian violet ink for purposes of orientation
5. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

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REVEAL 1 Trial
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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

Version 3.0

23 September 2016

Written by:

[redacted]

[redacted]
Date (DD-MMM-YYYY)

Reviewed and Approved by:

[redacted], MD, PhD

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

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[redacted], MD, PhD

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Date (DD-MMM-YYYY)

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27-Sep-2016

Date (DD-MMM-YYYY)

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Version 3.0

23 September 2016

Written by:

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Date (DD-MMM-YYYY)

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[redacted], MD, PhD

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

[redacted]

Date (DD-MMM-YYYY)

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HPV-301

REVEAL 1 Trial

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Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

EudraCT #2016-002761-63

Version 4.0

29 March 2018

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

Short Title: REVEAL 1 Trial (Randomized Evaluation of VGX-3100 and Electroporation for the treatment of Cervical HSIL)

Biological Product: VGX-3100

Protocol Number: HPV-301

Sponsor: Inovio Pharmaceuticals, Inc.
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Medical Monitor: [redacted], M.D., Ph.D.
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Inovio Pharmaceuticals, Inc.

SUMMARY OF CHANGES

The following is a list of protocol changes organized categorically and secondarily in order of appearance from HPV-301 protocol version 3.0 dated 23 September 2016 to HPV-301 protocol version 4.0 dated 29 March 2018.

1. The modifications and updates to the Hypothesis, Objectives and Endpoints are as follows:
    a. A footnote was added to the primary hypothesis for the purpose of clarification and alignment with the time frame for analysis.
    b. The wording of Secondary Endpoint 1b has been modified to more accurately state that all Adverse Events, not just SAEs will be reported through the entire duration that a subject is in the study.
    c. The wording of Secondary Objective 8 has been revised to more clearly reflect that immunology results are assessed relative to baseline levels.
    d. The Week 88 blood sample to test immune responses has been eliminated and the corresponding text has been removed from Secondary Objective 8.
    e. For Exploratory Objective 3, DNA methylation has been added to investigate as an additional potential biomarker.
    f. An Exploratory Endpoint 6 has been added to describe the association of a baseline tissue-based score derived using immunologic markers (Immunoscore) to the Week 36 efficacy endpoint.
2. The revisions to the Inclusion and Exclusion criteria are as follows:
    a. Inclusion criteria 1 has been revised to clarify that to be eligible, women must meet the minimum age of consent per local regulations, given that the age of consent can be older than 18 years in certain countries.
    b. Inclusion criteria 10(a) has been modified to align the definition of 'post-menopausal' with the medical literature, which defines postmenopausal as having amenorrhea for 12 months [1, 2].
    c. Exclusion criteria 3 has been clarified to reflect that patients who have a prior ECC that shows potentially untreated carcinoma (therefore, requiring more immediate treatment), or untreated HSIL, (i.e. a lesion that cannot be fully visualized) would be excluded.
    d. Exclusion criteria 7 has been revised to clarify that potential subjects with abnormal clinical screening laboratory values that resolve could qualify for screening. The window for use of clinical laboratory results at screening has been extended from 30 days to 45 days, which is still considered an acceptable acute time period but allows for screening activities to be completed with less risk of having to repeat blood draws during the screening period.
    e. For Exclusion criteria 8, malnutrition has been added to the list of potentially immunocompromising conditions.

f. For Exclusions 9 and 10, 'Day 0' has been changed to 'dosing' to more accurately reflect the applicability for all doses.

g. Exclusion criteria 12 has been modified to add the example of local anogenital malignancy that has been curatively treated.

3. Updates to the Schedule of Events Table have been made as follows:

   a. The screening window for dosing has been clarified as 10 weeks from the date of collection of biopsy.

   b. The assessment of AEs and SAEs has been added as a separate line item to the table to align with Section 6, Study Procedures and Treatments.

   c. Footnote (e) has been revised to reflect that the requirement of pregnancy testing is only for women of child bearing potential.

   d. Footnote (f) has been revised to clarify that 8 ml of serum should be collected only at Screening, Day 0 and Week 8.

   e. Footnote (k) has been revised to add clarifying details for the lesion photography process, (also as described in Sections 6.1.1, 6.2 and 6.13).

   f. Footnote (p) has been revised to reflect the addition of quality of life questions at the Week 40 phone call visit for subjects enrolled in United States of America (USA), Canada, Germany, Mexico and United Kingdom (UK) (also as described in Sections 6.2 and 6.8).

4. General updates and clarifications:

   a. For the Study Design Section in Clinical Protocol Synopsis, the term 'enrollment' has been replaced with the more specific term 'randomization' regarding the process of biopsy slide review by the Pathology Adjudication Committee (PAC).

   b. For the Section 2 (Study Design) and Section 8.2 (Randomization and Blinding), a statement has been added indicating that a group of sequential allocation numbers will be designated for use by each participating country.

   c. For Section 1.1.3 (Electroporation), the Table of Comparative Device Overview has been removed and a statement has been added referring to the VGX-3100 Investigator Brochure, where the most current information can be found.

   d. For Section 2.1.3 (Definition of Responder and Non-Responder), text describing the definitions of responder and non-responder for the primary endpoint has been added to correspond with the section table. Also, additional tables describing the definitions of responder and non-responder for the secondary efficacy endpoints have been added.

   e. In Section 5 (Sample Label for Investigational Product and Device), the device description has been updated to align with other study related documents (i.e. pharmacy manual, Investigator brochure).

f. In Sections 5.8 (CELLECTRA™ 5PSP Device) and 5.9 (Use of CELLECTRA™ 5PSP Device), the content has been updated to align with the VGX-3100 Investigator Brochure and Device User Manual.

g. For Section 6.1.1 (Screening Evaluations), ASCUS with or without a positive HPV test result has been substituted with ASC-H with or without a positive HPV test result to represent a higher probability condition that may qualify for screening.

h. Additional language to clarify the approach to lesion photography has been added to the study procedures and treatments sections, 6.1.1, 6.2 and 6.13, (in addition to the Schedule of Events Table footnotes)

i. Sections 6.1 (Before Treatment Procedures) and 6.2 (During Treatment Procedures by Visit) have been revised to align with the Schedule of Events Table.

j. For Section 6.3.3.10 (Subject Self Evaluation), additional guidance has been added regarding the assessment and reporting of events from Participant Diary Card (PDC).

k. For Section 6.4.1 (Risks of Treatment Procedures) has been revised to refer to the VGX- 3100 Investigator Brochure, which has the most current information.

l. Section 6.9 (Peripheral Blood Immunogenicity Assessments) has been revised to add information regarding the DNA methylation biomarker.

m. Section 6.10 (Tissue Immunogenicity Assessment) has been revised to add details regarding the Immunoscore analysis, which corresponds with Exploratory Objective 6.

n. Section 7.1. (Safety Parameters) has been revised as follows:

    i. For Section 7.1.3 (Unexpected Adverse Drug Reactions and Expedited Reporting), the guidance for assessing severity has been updated adding Grade 5 to align with the Common Toxicity Criteria for Adverse Events (CTCAE) grading scale.

    ii. For Section 7.1.9 (Procedures for Documenting Pregnancy during Study), has been modified to clarify the timing of reporting of pregnancy in the study (i.e. all pregnancies that occur from the time of first screening procedure must be reported) and correct a potential discrepancy in the prior version.

o. Section 7.3 (Safety and Toxicity Management) has been modified to align with safety assessments as stated in the section describing study design of clinical protocol synopsis.

p. Section 8 (Statistical Analysis Plan) has been revised to align with the changes made to Objectives and Endpoints as follows:

    i. Section 8.1 (General Considerations): details of microRNA and DNA methylation testing have been added.

    ii. Section 8.8 (Prior and Concomitant Medications) has been revised to clarify that the start dates for prior and concomitant medications will not be imputed.

iii. Section 8.9 (Efficacy Analysis) has been revised to add a description regarding the Immunoscore analysis per Exploratory Objective 6.

iv. Section 8.10 (Immunogenicity Analyses) has additional clarifying information regarding the evaluation of immune assays.

v. Section 8.11.1 (Adverse Events) has been revised to clarify the use of start and stop dates of adverse events for analysis purposes.

vi. Section 8.14 (Patient Reported Outcomes) has been revised to change the testing method from non-parametric or Miettinen and Nurminen to Wilcoxon rank-sum test or Pearson chi-square test/Fisher's exact test, which is appropriate for scales with multiple categories rather than only two categories.

q. Section 9.4.2 (Pathology Adjudication Committee) now refers to the PAC charter, which has the most current information regarding the PAC review process.

r. The Participant Diary Card is unchanged but has been removed from the Appendix since the Participant Diary Card is a separate document.

5. Additional minor grammatical and administrative changes have been made throughout the document for improvement of general readability.

INVESTIGATOR ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Investigator below constitute his/her approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, ICH-GCP guidelines, local legal and regulatory requirements as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____

Investigator – Signature Date (DD/MMM/YYYY)

_____

Investigator – Printed Name

Site Number: _____

Site Name: _____

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I LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
Baseline	Prior to first dose
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CMI	Cell mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
DNAme	Methylated Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation with CELLECTRA™ 5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LSIL	Low grade squamous intraepithelial lesion
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
miRNA	Micro Ribonucleic Acid
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

II CLINICAL PROTOCOL SYNOPSIS

Title of Study: 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)[1] of the Cervix	
Estimated Number of Study Centers and Countries/Regions: Approximately 125 Sites in up to 25 Countries	
Study Phase: 3	
Primary Hypothesis: Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL[Cervical Intraepithelial Neoplasia (CIN)2, CIN3] of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit[2]	
Study Drug Dose	6 mg (1 ml)
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device
Schedule	Day 0, Week 4, and Week 12 study visits
No. of Subjects	Approximately 198 subjects will be randomized in a 2:1 ratio to receive VGX-3100 or placebo
Study Duration	88 weeks
Primary Objective	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**
Primary Endpoint	Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsy or excisional treatment) and **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit

[1] Terminology based on 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP)
[2] The time frame is defined as any time starting from 14 days prior to the protocol-specified target date of Week 36

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of all adverse events including Serious adverse events (SAEs) (e.g. Suspected unexpected serious adverse reaction (SUSAR), Unexpected adverse device effect (UADE) and other unexpected AEs) for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by **virologic clearance of HPV-16 and/or HPV-18**	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by **complete histopathologic regression of cervical HSIL to normal**	4. Proportion of subjects with **no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both **complete histopathologic regression of cervical HSIL to normal and virologic clearance** of HPV-16 and/or HPV-18	5. Proportion of subjects with **no evidence of LSIL or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) **and no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Week 36 visit
6.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic non-progression**	6. Proportion of subjects with **no progression of cervical HSIL** to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response to VGX-3100 compared with placebo at post dose 3 and Week 36 visits as assessed relative to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15 and 36 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15 and 36 visits

	8c. Flow Cytometry response magnitudes at baseline and Week 15 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Evaluate effect of Human Leukocyte Antigen (HLA) type on efficacy	2. HLA (per-locus and per-allele basis) in conjunction with **histologic regression of cervical HSIL** at Week 36 visit
3. Describe association of microRNA (miRNA) profiles, DNA methylation profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	3. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits), miRNA profile (baseline, Week 8) and DNA methylation profile (baseline, Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe the durability of **virologic clearance of HPV-16 and/or HPV-18** for subjects treated with VGX-3100 compared with those treated with placebo	4. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Weeks 62 and 88 visits
5. Describe the patient-reported outcomes for subjects treated with VGX-3100	5. Patient-reported outcome questionnaires self-administered at baseline, after each dose at Weeks 4, 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK
6. Describe the association of a tissue-based score derived using immunologic markers (Immunoscore) at baseline to histological and virological response to VGX-3100 at Week 36	6. Immunoscore results for VGX-3100 treated subjects in conjunction with histological and virological outcomes at Week 36

Study Design:

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled Phase 3 study to determine the efficacy safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16 and/or HPV-18 (HPV-16/18). The composite primary endpoint is histologic regression of cervical HSIL, and clearance of the underlying HPV-16/18 infection. A sample of

approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

To be eligible for the study, women age 18 years and above must consent to participate and have biopsy/biopsies of the cervical lesion(s) at the time of screening. The biopsy slides are sent to a central pathology lab for Pathology Adjudication Committee (PAC) review in a blinded manner to establish the presence of cervical HSIL (CIN2, CIN3) prior to randomization. Subjects must also have a cervical ThinPrep™ specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

All eligible subjects will receive three doses of VGX-3100 or placebo administered IM followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment is administered on Day 0, the second at Week 4, and the third (final) study treatment is administered at Week 12. The first dose is administered as soon as possible following confirmation of the cervical HSIL diagnosis and cervical sample positive for HPV-16/18 but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening.

Subjects are randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (c) age category (<25 years vs. ≥25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

The long term follow up plan following the Week 36 efficacy assessment will include safety, cytology and HPV testing for a period of approximately 1 year (Week 88).

Efficacy: Visualization of a normal appearing cervix by colposcopy and cytology are insufficient evidence to confirm disease regression. Therefore, disease regression will be based on histopathological assessment, which is considered the definitive method for diagnosis. Subjects will also be assessed by colposcopy, cytology, and HPV testing at screening, and at specified visits on and after Day 0. Digital photographs of the cervix following application of acetic acid will also be used to document colposcopic exam findings.

Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (e.g. loop electrosurgical excision procedure (LEEP), large loop excision of transformation zone (LLETZ), cold knife conization (CKC)) or by biopsy (4 Quadrant Biopsy or 4 Quadrant Biopsy with Endocervical Curettage (ECC)) based upon the assessment at Week 28 of cytology, High Risk (HR) HPV status, and colposcopic findings (see Tables 5 and 6, for Minimally Required Procedures).

Safety: All subjects will be followed for 88 weeks.

Subjects will be monitored for:

1) Local and systemic events for 7 days following each investigational treatment as noted on a Participant Diary Card (PDC);
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

Data and Safety Monitoring Board (DSMB): The DSMB will meet quarterly to review unblinded safety data and histopathologic regression results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with histopathologic regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed.

Immunogenicity: Humoral and cell mediated immune responses in response to VGX-3100 treatment will be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks15, and 36. Cervical tissue samples will also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

Virology: Cervical cytology samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 8, 15, 28, 36, 62, and 88 by cobas™ HPV test. Additionally, if there is residual tissue in the paraffin block from cervical tissue after histologic diagnoses have been rendered at screening and Week 36, then unstained slides and/or the relevant paraffin blocks may be tested for the presence of HPV-16/18. Vaginal brush and oropharyngeal rinse samples will be obtained at Day 0 (prior to dosing), Weeks 36 and 88 while intra-anal samples will be obtained on Day 0 (prior to dosing) and Week 36 to characterize HPV infection.

HLA typing: The relationship between subject HLA types and efficacy responses will be explored using available PBMC sample collected for immunogenicity analysis.

Study Population

Inclusion Criteria:

1. Women aged 18 years and above and meets the minimum age of consent per local regulations;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas™ HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:

a) Post-menopausal as defined by spontaneous amenorrhea for more than 12 months;
b) Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
c) Women of Child Bearing Potential (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable :
    i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
    ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
    iii. Intrauterine device or intrauterine system;
    iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;

11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

Exclusion Criteria:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
3. ECC that shows a potentially untreated carcinoma, untreated HSIL, indeterminate, or insufficient for diagnosis (ECC is not required to be performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant through Week 36 visit;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Silgard™, Cervarix™);
7. Presence of any unresolved abnormal clinical screening laboratory values of Grade 1 or greater per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 and deemed clinically significant by the investigator within 45 days prior to Day 0;
8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 30 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;

f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results
g) Subjects who are malnourished (i.e. medically significant unintentional weight loss, kwashiorkor, or marasmus) based on screening labs, medical history and physical exam per the investigator's clinical judgment.

9. Receipt of any non-study, non-live vaccine within 2 weeks of dosing;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of dosing;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
12. Malignancy or systemic treatment for malignancy within 2 years of screening (with the exception of curatively treated, localized anogenital cancers and superficial skin cancers which are permitted)
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Table 1. Schedule of Events

Tests	Screening (-10 weeks to -1 Day from Date of Biopsy)	Weeks												
		Day 0	8-14 days post Day 0 Phone Call	4 (± 4 days)	8-14 days post Week 4 Phone Call	8 (± 4 days)	12 (± 4 days)	8-14 days post Week 12	15 (± 1 week)	28 (± 1 week)	36 (± 1 week)	40 (± 2 weeks) Phone call	62 (± 2 weeks)	88 (± 2 weeks)
Informed consent	X													
Medical History	X													
Demographics	X													
Socio-behavioral[a]	X										X			X
Inclusion / Exclusion	X	X												
Randomization		X												
Physical exam/assessment[b]	X	X		X		X	X		X	X	X		X	X
Vital signs	X[c]	X		X		X	X		X	X	X		X	X
Screening safety[d]	X													
Pregnancy Test[e]	X	X		X			X		X	X	X		X	X
HIV Antibody Testing	X													
Blood immunologic samples[f]	X	X				X			X[g]		X			
Cervical Digene swabs[i,j]	X	X							X	X	X			X
ThinPrep™ [h,i]	X	X				X			X	X	X		X	X
Colposcopy, lesion photograph[k]	X[l]	X							X	X	X		X	X
Ectocervical biopsy[m]	X										X[n]			
Surgical excision[m]											X[n]			
OP rinse, vaginal swabs		X									X			X
Intra-anal swabs[o]		X									X			
Inject VGX-3100/Placebo		X		X			X							
Post treatment assessment		X	X	X	X	X	X	X[q]	X					
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Distribute PDC		X		X			X							
Review PDC			X		X	X		X[q]						
PROs[p]		X	X	X	X		X	X[q]		X	X	X		X

[a] Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

[b] Full physical examination (PE) mandatory at screening and study discharge (Week 88), otherwise targeted physical assessment as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

[c] Screening vital signs must include a measured height and weight. Weight will be collected on Day 0, Weeks 4 and 12;

[d] Screening safety includes 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 45 days prior to Day 0;

[e] For WOCBP, a negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

[f] At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood per time point and 8 mL serum per time point at Screening, Day 0 and Week 8 (4 ml serum per time point at Week 15 and 36). A total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0. HLA testing will performed once from an existing PBMC sample;

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

[i] Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

[j] Collected prior to the ThinPrep™ sample;

[k] A photograph of the lesion with at least one attempt should done as follows: Acetic acid should first be applied to the cervix then photographs of the cervix and the associated lesion should be photographed prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit.

[l] Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy;

[m] Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 5 and 6);

[n] Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from screening and/or Week 36 specimen(s) (paraffin blocks or unstained slides) may be used for immunohistochemistry (IHC) and HPV testing;

[o] To be collected only if subject consents for intra-anal sample collection

[p] One or both PRO questionnaires (i.e. SF-36 and EQ-5D-5L) will be completed by subjects enrolled in USA, Canada, Mexico, Germany and UK at multiple visits during the study. Additional quality of life questions will be asked at the Week 40 phone call. Refer to Section 6.8 for details

[q] Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 HPV INFECTION, CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [3]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a HR HPV type [4, 5]. Up to 13000 women in the US alone are diagnosed with cervical cancer each year, which leads to an estimated 4120 deaths [6]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two genotypes are estimated to cause about 70% of all cervical cancers [7, 8].

Incident infection by HPV is characterized by ongoing viral replication and shedding and is associated with early histologic changes (grade 1 cervical intraepithelial neoplasia) when the female cervix is infected with HPV. Most cases of genital HPV infection clear spontaneously, but persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions of the cervix, HSIL which is inclusive of grade 2 and 3 cervical intraepithelial neoplasia (CIN2/3) [9]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [10, 11]. The basis for these changes are attributed to the viral proteins E6 and E7. Infected cells produce E6 and E7 constitutively which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia.

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade CIN caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [12]. This means that the large number of women who already have high grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they didn't respond to vaccination, must currently only rely upon surgery and the chance of spontaneous regression to treat their condition and avoid progression to cancer. Furthermore, the number of US-eligible teenagers who complete the prophylactic vaccination series remains low; 39.7% of US girls ages 13-17 completed their prophylactic HPV immunization series in 2014, which leaves a potentially vulnerable, under-protected population [13]. The current approaches to the management of cervical HSIL typically require surgery (i.e. LEEP/LEETZ, laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100 is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

1.1.2 VGX-3100

VGX-3100 contains plasmids that encode HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was water for injection with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This WFI/LGS formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100[3] was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This SSC formulation of VGX-3100 was administered to 116 subjects in a Phase 1 clinical trial, HPV-101. In study HPV-101, three 6 mg doses of VGX-3100 as the SSC formulation were delivered IM followed by EP with CELLECTRA™ 5P to healthy adults. Based upon interim analysis data at study Week 14, the SSC formulation is considered non-inferior to the WFI/LGS formulation based upon a 2-fold rise in overall Spot Forming Units (SPU) to the antigens encoded by the plasmids per 10^6 Peripheral Blood Mononuclear Cells (PBMC) as measured from baseline to Week 14 using the interferon-γ ELISpot assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (WFI/LGS formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or HPV-18. The Phase 2b study, HPV-003, enrolled and dosed 167 subjects with high grade cervical dysplasia from seven countries and one United States Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, United States and Puerto Rico). Subjects were randomized in a 3:1 ratio to the treatment arm (VGX-3100, WFI/LGS formulation) or the placebo arm, respectively. All subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to CIN1 or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol and modified intent to treat analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.3 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses

[3] Designated in earlier version of the HPV-301 protocol as VGX-3100X

creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity

[14, 15]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [16, 17]. This technology has been used for more than three decades by molecular biologists for cell transfection and has demonstrated versatility in use, as shown by its functionality in combination with a range of molecules, tissue types, disease indications, and across species [18].

The CELLECTRA™ device developed by Inovio is used for investigational purposes to administer plasmid-based DNA, in both prophylactic and therapeutic settings. Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency, and has demonstrated that the device helps to elicit favorable immunogenicity in several species (e.g., mice, pigs, and rhesus macaques) [19, 20].

VGX-3100, WFI/LGS formulation, has been administered throughout Phase 1 and Phase 2 investigations with the CELLECTRA™ 2000 device. A next generation device, CELLECTRA™ 5PSP, will be used in Phase 3. Both designs of the CELLECTRA™ device enhance the intracellular uptake of VGX-3100 by the delivery of electrical current, and the electrical current delivery and pulse pattern (electroporation) is identical in both designs. CELLECTRA™ 2000 involves a manual injection of VGX-3100 while the CELLECTRA™ 5PSP device will automate the intramuscular delivery of VGX-3100 and delivery of the EP pulses triggered by a single button press. Neither the dosage nor volume of VGX-3100 administered differs between the two devices. Administration of VGX-3100 with the CELLECTRA™ 5PSP also allows selection of the array needle length (13, 19 or 25 mm) depending on the estimate of the recipient's subcutaneous fat and muscle tissue.

The technology differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design are not significant and do not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, environmental specifications, and sterilization or performance specifications. The material changes are to the outer housing of the device and not to patient-contacting materials.

Benchtop design verification testing and a non-significant risk device functionality study will be completed prior to Phase 3 to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™ 5PSP device design meeting its safety and performance specifications, and no change to the administration of VGX-3100 by electroporation. Inovio's device experience demonstrates that delivery of electroporation pulses into muscle immediately following injection of DNA plasmids is well-tolerated in humans and no significant safety issues have been identified [21-23]. For further information concerning the 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.4 SELECTION OF STUDY DESIGN

This Phase 3 study employs a prospective, randomized, double-blind, placebo controlled study design to further demonstrate the safety and efficacy of VGX-3100 followed by EP in women with cervical HSIL associated with HPV-16/18. The primary clinical hypothesis is that VGX-3100 is a surgery-sparing, therapeutic option for the treatment of cervical HSIL and the underlying,

pathogenic HPV-16/18 infection, which is supported by the findings of the Phase 2b trial. A placebo-controlled study is selected for this trial because it provides scientific rigor to distinguish an effective treatment, particularly in cervical HSIL for which spontaneous regression does occur.

1.2 DOSE AND REGIMEN RATIONALE

A total dose of 6 mg VGX-3100 DNA has been selected for this study based on previous human experience with both the WFI/LGS and SSC formulations of VGX-3100, preclinical data with VGX-3100 and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 2) without significant safety issues [21].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a true effect rather than random variation. Adverse events from previous human studies with VGX- 3100 (frozen formulation) and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in the Phase 2b study. The results obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Table 2. Percent of Protocol HPV-001 Subjects Responding and Average SFU/10^6 PBMC in Responders for each Antigen by Cohort in Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	%Response	AVG	%Response	AVG	%Response	AVG
HPV-16E6	33%	107	50%	243	50%	1341
HPV-16E7	17%	198	50%	104	67%	143
HPV-18E6	50%	359	50%	338	83%	664
HPV-18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

1.3 RISKS/BENEFIT ASSESSMENT

1.3.1 RISKS ASSOCIATED WITH CURRENT THERAPEUTIC OPTIONS

Currently, treatment of women with cervical HSIL usually consists of either surgical removal of the affected tissue by CKC, LEEP, ablative therapy via laser, or cryotherapy. All treatments for

cervical HSIL are associated with a variety of short and long term general and reproductive health risks as listed in Table 3.

Table 3. Risks Associated with Surgical Treatments for Cervical HSIL

Surgical Treatments for Cervical HSIL	**Risks**
CKC LEEP Ablative therapy (Laser or Cryotherapy)	Pain
	Exposure to anesthesia
	Heavy bleeding
	Infection
	Menstruation problems
	Cervical stenosis (can lead to alteration of squamo-columnar junction)
	Shortening of the cervix
	Decreased fertility/difficulty getting pregnant
	Cervical incompetence
	Pre-term birth and related low birth weight
	Incomplete treatment of cervical dysplasia
	Inadequate treatment of an occult early invasive cancer

Adapted from *FAQs Loop Electrosurgical Excision Procedure (LEEP) American College of Obstetricians and Gynecologists (2014) [13]*.

More importantly, none of the currently available surgical treatments for cervical HSIL eradicate the underlying cause of the high grade cervical dysplasia, persistent infection with one or more of the high-risk HPV types, and therefore, leaves patients at risk for recurrent cervical HSIL as well as high grade dysplasia of the vulva and vagina due to the potentially broader infection of the genitourinary area.

Although professional guidelines typically advocate immediate excisional therapy for adults with cervical HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [10]. The risk of a "missed diagnosis" of an occult early invasive cervical cancer exists for all current treatment modalities including surgical and ablative therapies. Furthermore, approximately 17-18% of patients with high grade CIN will experience recurrence of dysplasia following surgical intervention [10], which illustrates that current standard of care for cervical dysplasia requires improvement. The study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult early invasive cervical cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent cervical colposcopy, cytology and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced gynecologists, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

1.3.2 POTENTIAL RISKS OF STUDY PARTICIPATION

A risk associated with VGX-3100 for the treatment of high grade cervical dysplasia are the injection site reactions related to the IM injection and/or electroporation. Based on the phase 1

and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild (e.g. erythema) and limited to a few days in duration at most.

A second risk is the "delay" in "definitive treatment" of the high grade cervical dysplasia and the "missed diagnosis" of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not spontaneously regress. This risk is mitigated by careful serial cytology, HPV testing, and colposcopic exams, throughout the course of the study, and the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. Also, only investigators who are experienced in the management of cervical cancer will be chosen, and they will have the option of performing additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression.

A DSMB will also advise the Sponsor if it appears that the frequency of regression in the VGX-3100 group is unacceptably low compared to the placebo group. These measures should minimize the risk - even perhaps below that of standard care - of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. All subjects with suggestion of residual disease will undergo excisional therapy (e.g. CKC, LLETZ, LEEP) at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Tables 5 & 6) to provide histopathologic confirmation of regression. In the Phase 2b study, the rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [24].

1.3.3 POTENTIAL BENEFITS OF STUDY PARTICIPATION

All currently accepted treatments for high grade cervical dysplasia are surgical procedures (LEEP, CKC, Laser ablation) which are all associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding and/or infection, damage to other organs, shortening and/or deformation of the cervix, pain, etc. Due to the risk of shortening and/or deformation of the cervix there are additional well accepted risks including cervical stenosis, infertility, cervical incompetence, preterm birth, and inability to visualize the transformation zone. Additionally, none of the surgical treatments systemically address the underlying oncogenic root cause, the high risk HPV infection in the lower genital tract, which leaves an underlying risk for further disease manifestations and transmission of HPV. VGX-3100+ EP is not associated with any of the risks associated with the surgical procedures outlined above (except for pain, which is transient and restricted to the deltoid/quadriceps treatment site) and has demonstrated the ability to not only eradicate the high grade dysplasia but also the ability to eradicate the underlying HPV infection. Subjects receiving placebo, who represent women of child-bearing potential, may benefit from the opportunity to be closely managed under careful surveillance over the course of this study and those who regress spontaneously will be able to avoid excisional therapy.

2 STUDY DESIGN

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled study to determine the efficacy, safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18.

A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

Subjects will be randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category ($\leq$25 vs. >25 kg/m^2), and (c) age category (<25 years vs. $\geq$25 years). To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of cervical HSIL. Subjects must also have a cervical specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

2.1 ENDPOINT ASSESSMENT

In the Phase 2b study, subjects were randomized 3:1 to the VGX-3100 frozen formulation arm or the Placebo arm. All subjects were scheduled to receive treatment on Day 0, Week 4 and Week 12 and undergo repeat cervical biopsy or surgical excision (i.e. LEEP, LLETZ, CKC) of the cervix at Week 36 to assess efficacy. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit, and the secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less.

The primary endpoint for the Phase 3 study is based upon the results of the Phase 2b study. Given that HPV persistence is an important factor in the clinical progression of dysplasia and also based upon the findings of the secondary objective of the Phase 2b study, the responder definition for the Phase 3 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16/18.

The proportion of subjects who achieved this endpoint in the Phase 2b study was 35% (40%) of VGX-3100 subjects versus 14% (15%) for placebo, in an intention-to-treat analysis and modified intention-to-treat analysis, respectively. The composite endpoint of histologic regression and virologic clearance will be primary in the Phase 3 study, and histologic regression endpoint will be a secondary endpoint.

2.1.1 HISTOLOGY ASSESSMENT

Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Digital photographs of acetowhite lesions are also used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or by 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings as outlined in Tables 4 and 5 for subjects 25 years and above and below 25 years, respectively.

Table 4. Minimally Required Procedure at Week 36 for Subjects Age 25 Years and Above

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
25 and above	NA	NA	HSIL, ASC-H, AGC, Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	positive	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	negative	4Q biopsy and ECC
	unsatisfactory	no lesion	NILM	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Table 5. Minimally Required Procedure at Week 36 for Subjects Under 25 Years

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
18-24	NA	NA	Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	HSIL, ASC-H, AGC	NA	Tissue Excision
	unsatisfactory	no lesion	NILM, ASC-US, LSIL	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US, HSIL, ASC-H, AGC[b]	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] Any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

[b] If cytology result is AGC "favor neoplasia", tissue excision is recommended

2.1.2 VIROLOGIC (HPV) ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28, 36, 62, and 88. Also, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for testing of HPV-16/18. Vaginal and oropharyngeal samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 36, and 88 to assess virologic response to treatment at sites other than the cervix. Intra-anal samples will be obtained (if subject consents to intra-anal sampling) to characterize HPV infection at Day 0 (prior to dosing) and at Week 36 to assess virologic response to treatment at sites other than the cervix.

2.1.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 6) for the primary endpoint takes into account both histopathologic regression of cervical HSIL and virologic (HPV-16 and/or HPV-18) clearance from cervical samples since HPV persistence is an important factor in the clinical progression of HSIL. The responder definition also excludes subjects whose cervix is biopsied at any time between their initial biopsy to determine eligibility and the Week 36 endpoint tissue collection. This exclusion is included to reduce the potential for artefactual increases in the treatment effect caused by removal of HSIL tissue and potentially HPV-16/18 by unplanned interval biopsies.

To qualify as a responder, the subject must have:

1. An acceptable histology specimen at Week 36, which is interpretable by the independent PAC, and
2. An acceptable HPV ThinPrep™ sample at Week 36, with an associated valid HPV-testing result.

A responder is defined as a subject with:

1) No histologic evidence of cervical HSIL
2) No evidence of HPV-16 and/or HPV-18 at the Week 36 evaluation
3) The subject must not have had an unscheduled cervical tissue sample obtained between Screening and the Week 36 evaluation.

Conversely, the following will designate the subject as a non-responder:

1) Histologic evidence of cervical HSIL at the Week 36 evaluation, OR
2) Evidence of HPV-16 or HPV-18 at the Week 36 evaluation, OR
3) A cervical tissue sample obtained between Screening and the Week 36 evaluation OR
4) Lack of either an acceptable Week 36 histology specimen or HPV ThinPrep™ sample.

Table 6. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 and/or HPV-18 at Week 36[b] AND Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, or cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 primary endpoint visit OR Subject with no Week 36 primary endpoint sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL
[b] The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal within the time frame determines the HPV clearance endpoint.

Responder and non-responder definitions for the secondary efficacy endpoints are detailed in Table 7 – Table 11.

Table 7: Definition of Secondary Regression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 visit[b] **AND** Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 visit **OR** Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL
[b] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.

Table 8: Definition of Secondary Complete Regression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL squamous atypia, or LSIL at Week 36 visit[a] **AND** Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 visit	Subject with histologic evidence of cervical HSIL, squamous atypia, LSIL, AIS, cervical carcinoma at Week 36 visit **OR** Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.

Table 9: Definition of Secondary Non-progression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of a worsening of cervical condition at Week 36 visit[a] relative to baseline **AND** Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 visit	Subject with histologic evidence of worsening of cervical condition at Week 36 visit relative to baseline **OR** Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.

Table 10: Definition of Secondary Complete Regression and Clearance Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL, squamous atypia, or LSIL[a] at Week 36 visit and no evidence of HPV-16 and/or HPV-18 at Week 36 visit[b] **AND** Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 visit	Subject with histologic evidence of cervical HSIL, squamous atypia, or LSIL AIS, cervical carcinoma at Week 36 visit **OR** Subject with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

[b] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal within the time frame determines the HPV clearance endpoint.

Table 11: Definition of Secondary Clearance Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of HPV-16 and/or HPV-18 at Week 36 visit[a] **AND** Subject in which a cervical tissue sample was NOT obtained between collection of tissue to determine entry eligibility up to Week 36 visit	Subject with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in which an additional cervical tissue sample was obtained between collection of tissue to determine entry eligibility up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone HPV testing at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal within the time frame determines the HPV clearance endpoint.

2.1.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100 treatment will be evaluated in blood samples taken at baseline (both screening as well as Day 0 prior to dosing) and at Weeks 15, and 36. Cervical tissue samples will also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Whenever possible, these studies may be performed on tissue sections from the diagnostic screening biopsy (pre-dose) and from tissue obtained post-dose(s) (Week 36).

2.2 TREATMENT PLAN

The three dose regimen of VGX-3100 appeared to be safe and well tolerated in the Phase 2b study, therefore all eligible subjects who consent to participate in the Phase 3 study will receive the same three 6 mg doses of VGX-3100 refrigerated formulation or placebo administered in 1 mL IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third (final) study treatment will be administered at Week 12 which is consistent with the Phase 2b study. The first study treatment will be given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16/18 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-16/18.

2.3 SAFETY MONITORING PLAN

Although cervical HSIL is thought to require years to progress to cervical cancer, subjects in the Phase 2b study were followed closely throughout. HPV testing (Weeks 14 and 24), cytology (Week 14) and colposcopy (Week 24) were all mandatory during the observation period prior to obtaining tissue for determination of the primary histologic endpoint at Week 36. Investigators were also instructed to perform additional testing (including biopsy) if disease progression was suspected. These instances were infrequent as only 11 unscheduled biopsies were deemed necessary over the course of the Phase 2b study. In addition, the rate at which occult microinvasive cancer was discovered after 36 weeks was less frequent than what is reported in the literature [24]. Both observations would imply that the mandatory monitoring employed in the Phase 2b study was sufficient; however cervical disease will be monitored even more closely in this Phase 3 study. Colposcopy, cytology and HPV testing will be required at 8 to 14 week intervals throughout the observation period leading up to the primary endpoint 36 weeks after the first dose. Although less frequent monitoring may be adequate, the more frequent monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy.

Safety monitoring will include:

- Local and systemic events for 7 days following each treatment as noted on a Participant Diary Card (PDC).
- All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

In the Phase 2b study, the safety profile was carefully evaluated and treatment with VGX-3100 was well-tolerated based on observations through Week 88 in all subjects. The most common adverse events were administration-site reactions, which included pain, tenderness, erythema and swelling, and were generally mild and limited to a few days in duration. Only erythema showed a statistically higher incidence in VGX-3100 (78%) vs. placebo (57%) in the 7- and 28-day periods after a dose. One additional AE, sinusitis, was also statistically significantly increased over the course of the entire study period but resolved without sequelae in the VGX-3100 arm compared to the Placebo arm (10% vs. 0%).

As outlined above, safety monitoring and visit frequency has been designed to take into account the potential risk of delay in the usual treatment of the high grade cervical dysplasia and also the potential for a missed diagnosis of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not regress. Serial cytology, HPV testing, and colposcopic exams are applied throughout the course of the study with the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. All subjects with suggestion of residual disease will undergo excisional therapy by LEEP or CKC at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Table 5 and 6) to provide histopathologic confirmation of regression. The use of a 4 quadrant biopsy in Phase 3 is a change from the approach used in Phase 2b to optimize the evaluation of histopathologic regression taking into consideration the inherent limitations of colposcopy and tissue biopsy samples in the absence of visible lesions [25].

In the Phase 2b study, the cervical tissue sample was initially read by a local pathologist and/or central pathology laboratory for rapid local medical management. The definitive histopathologic assessment was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US. Seven reports included the terms '(adeno)squamous cell carcinoma' or the premalignant condition of 'adenocarcinoma in situ' (AIS) in the final Phase 2b study results which included all 88 weeks of follow up. Three of the cases were reported as AIS, (2 VGX-3100, 1 placebo), out of which two cases (1 VGX-3100, 1 placebo) were confirmed as AIS by the Pathology Adjudication Panel. AIS is a pre-invasive glandular lesion which can be difficult to capture on standard of care screening with initial punch biopsy and is more commonly identified by full excision (e.g. LEEP, conization). There were four reports that included the term squamous cell carcinoma, of which two were confirmed by the Pathology Adjudication Panel, both in the VGX-3100 group. The other two cases (1 VGX-3100, 1 placebo) were diagnosed as CIN3 by the Pathology Adjudication Panel. The rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [24].

Importantly, investigators in the Phase 3 study will be chosen only if they are experienced in the management of cervical cancer as was the case in the Phase 2b study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a

non-responder in the efficacy analysis as outlined in Table 6. These measures should minimize the risk of progression of cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. The frequency of close monitoring by experienced investigators should minimize the risk of cancer progression on the study what is expected with standard of care.

2.3.1 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will be scheduled to meet quarterly. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with regression in the VGX-3100 group is unacceptably low compared to the placebo group. However, no formal interim analysis will be performed.

2.4 LONG TERM FOLLOW UP PLAN

In the Phase 2b study, all subjects were scheduled to be followed for 1 year after the histopathologic assessment for the primary endpoint (to study Week 88). The establishment of efficacy based on histopathologic evidence dictated the removal of tissue at week 36 by either punch biopsy (ies) or more extensive surgical resection (i.e. LEEP, CKC). Subjects with colposcopic evidence of residual disease were to undergo LEEP/CKC. A higher proportion of patients who received placebo had a LEEP performed than those who received VGX-3100 (Table 12).

Cytology and HPV-16/18 clearance from the cervix was to be assessed at study Weeks 62 and 88 to evaluate for recurrence of dysplasia and HPV infection after removal of tissue at Week 36. Overall, in the phase 2b study, the majority of subjects had improved cytology and had cleared their underlying HPV-16/18 cervical infection by the Week 62 and 88 visits. For Weeks 62 and 88, there were no clinically meaningful differences noted between the subjects who received an excisional treatment (e.g. LEEP, CKC) and those that showed histopathologic regression and therefore only underwent a biopsy, as shown in Table 8 which summarizes the HPV and cytology results following Week 36.

Table 12. HPV-003 HPV and Cytology Results at Weeks 36, 62 and 88, mITT Population

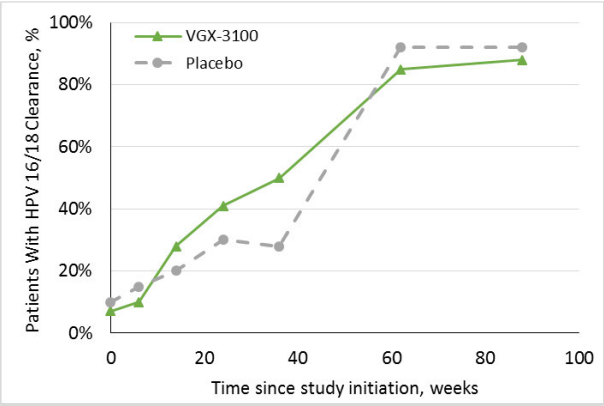
Week	Test[a]	VGX-3100		Placebo	
		LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	100% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89% (42/47)	89% (24/27)	100% (10/10)
88	Pap	96% (52/54)	91% (43/47)	85% (23/26)	100% (11/11)

Abbreviations: NA, not applicable, Pap smear was not done at Week 36
[a] HPV = HPV-16/18 testing; Pap = cytology testing
[b] LEEP or CKC done, at or before the study week as specified
[c] Only biopsy done, at or before the study week as specified

Clearance of HPV-16/18 from the cervix was observed in both treatment groups (Figure 1a) at similar rates until after the second dose when clearance in the VGX-3100 recipients continued to rise while the rate appeared to plateau in the placebo group.

Figure 1. HPV-16/18 Clearance and Pap Smear Findings in Phase 2b mITT Population by Treatment Group

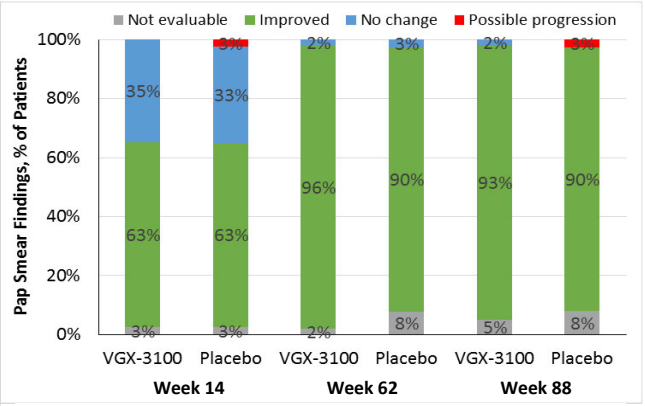
a.



No. of subjects

VGX-3100	123	62	118	116	115	108	103
Placebo	42	26	40	40	40	39	37

b.



No. of subjects

VGX-3100	118	108	103
Placebo	40	39	37

At Week 36, clearance was significantly higher among VGX-3100 subjects that had biopsy (63%) versus LEEP/CKC (41%), which likely reflects the association between clearance of the underlying HPV infection and the likelihood of having signs indicative of regression by colposcopic exam. HPV-16/18 clearance data (mITT population) post-Week 36 are described as follows: HPV-

16/18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% (42/51) for VGX-3100 post Biopsy only, 96% (27/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post Biopsy only. HPV-16/18 clearance at Week 88 was 89% (48/54) for VGX-3100 post-LEEP/CKC, 89% (42/47) for VGX-3100 post Biopsy only, 89% (24/27) for Placebo post-LEEP/CKC, and 100% (10/10) for Placebo post Biopsy only.

The majority of subjects had cleared their underlying cervical HPV-16/18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups. Forty-seven of 53 (89%) and 46 of 49 (94%) subjects at Weeks 62 and 88, respectively (mITT population) with histopathologic evidence of CIN2/3 regression (regressors) in the VGX-3100 treatment group experienced HPV-16/18 clearance. Despite the use of therapeutic resection for many VGX-3100 recipients whose CIN2/3 did not regress by Week 36 (non-regressors), HPV-16/18 clearance rates were notably lower (85% at Week 88) compared to regressors.

In the subjects who initially cleared HPV-16/18 by Week 36, only one HPV-16/18 recurrence was identified at the Week 62 and 88 evaluations. Specifically, one subject in the VGX-3100 group whose lesion was biopsied at Week 36 had HPV types 16 and 82 and CIN2 at screening, was HPV negative at Week 36, but tested HPV type 16 positive at Week 62, and then cleared HPV-16 at Week 88. The subject showed histopathologic regression at Week 36. No recurrences were identified in the eleven subjects in the placebo group whose lesions were biopsied at Week 36 with valid HPV data at Weeks 62 or 88. There were no (0/51) recurrences identified in the VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk as compared to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear cytology results at Week 62 were 93% (52/56) for VGX-3100 post-LEEP/CKC, 100% (51/51) for VGX-3100 post-Biopsy only, 93% (26/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post-Biopsy only. At Week 62, cytopathologic improvement was reported for 104 of 125 (83%) subjects in the VGX-3100 treatment group and 34 of 42 (83%) subjects in the placebo treatment group (mITT population).

There were no instances of possible progression, and all cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. Improvement compared to study entry for Pap smear cytology results at Week 88 were 96% (52/54) for VGX-3100 post-LEEP/CKC, 91% (43/47) for VGX-3100 post-Biopsy only, 85% (23/26) for Placebo post-LEEP/CKC, and 100% (11/11) for Placebo post-Biopsy only. At Week 88, possible progression (atypical glandular cells) was reported in a single Placebo subject in the post-LEEP/CKC group (3%) and no subjects treated with VGX-3100. All other cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. The majority of subjects showed improvement, and there was no meaningful difference between the Week 62 and Week 88 evaluations. These findings support that study subjects had no increased risk of progression based upon cytology as compared to standard of care.

The protocol-specified removal of dysplastic cervical tissue at Week 36 by either method substantially affected the clearance of HPV-16/18 and normalization of cytologic findings as expected, regardless of treatment group (Figure 1a, b). HPV-16/18 clearance rises at a sharp rate

after tissue is removed at Week 36 whether the excision is wide (e.g. LEEP, LLETZ, CKC) or more limited (biopsy). Notably, the method of tissue collection at the Week 36 endpoint did not appreciably affect the HPV-16/18 clearance rates beyond Week 36 (Table 8). Based upon the Phase 2b results, the risk of progression or recurrence of cervical dysplasia is low and comparable to the rates observed post-LEEP/CKC in clinical practice. The long term follow up planned for this Phase 3 study will include safety, cytology and HPV-16/18 testing at 6 months and also 1 year following the Week 36 histopathologic assessment, which is highly conservative given the expectation that few subjects will have persistent evidence of disease after the removal of tissue at Week 36 which is supported by the findings in the Phase 2b study.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 HYPOTHESIS

Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered IM followed by EP with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16/18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit.[4]

3.2 PRIMARY OBJECTIVE AND ENDPOINT

Objective	**Endpoint**
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	Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit

[4] The time frame is defined as any time starting from 14 days prior to the protocol-specified target date of Week 36.

3.3 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of all adverse events including SAEs (e.g. SUSAR, UADE and other unexpected AEs) for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6.Determine the efficacy of VGX-3100 compared with placebo as measured by histopathologic non-progression	6. Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (i oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response to VGX-3100 compared with placebo at post dose 3, and Week 36 visits as assessed relative to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15, and 36 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, and 36 visits 8c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.4 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Endpoints
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Evaluate effect of HLA type on efficacy	2. HLA (per-locus and per-allele basis) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Describe association of microRNA (miRNA) profiles, DNA methylation profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	3. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits), miRNA profile (baseline, Week 8) and DNA methylation profile (baseline, Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
4. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100 compared with those treated with placebo	4. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
5. Describe the patient-reported outcomes for subjects treated with VGX-3100	5. Patient-reported outcome questionnaires will be self-administered at baseline, Weeks 4, and 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK.
6. Determine whether a tissue-based score derived using an immunologic markers (Immunoscore) at baseline is predictive for histological and virological response to VGX-3100 at Week 36	6 Immunoscore results for VGX-3100 treated subjects and in conjunction with histological and virological outcomes at Week 36

4 SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Women aged 18 years and above and meets minimum age of consent per local regulations);
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas^{TM} HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;

5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) WOCBP is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
        iii. Intrauterine device or intrauterine system
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject
11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from enrollment in the study:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
3. ECC shows a potentially untreated carcinoma, untreated HSIL, indeterminate, or insufficient for diagnosis (ECC is not required to be performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant through Week 36 visit;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Silgard™, Cervarix™);

7. Presence of any unresolved abnormal clinical screening laboratory values of Grade 1 or greater per CTCAE v 4.03 and deemed clinically significant by the investigator within 45 days prior to Day 0;
8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 30 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
    g) Subjects who are malnourished (i.e. medically significant unintentional weight loss, kwashiorkor, or marasmus) based on screening labs, medical history and physical exam per investigator's clinical judgment.
9. Receipt of any non-study, non-live vaccine within 2 weeks of dosing;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of dosing;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
12. Malignancy or systemic treatment for malignancy within 2 years of screening (with the exception of curatively treated, localized anogenital cancers and superficial skin cancers which are allowed);
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;

20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests Grade 3 toxicity attributable to the study treatment, the medical monitor and Investigator will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All randomized subjects should be encouraged to complete all study treatments and follow-up visits. A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule for follow-up and treatment of HSIL (CIN2, CIN3), and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/ WITHDRAWAL

The investigator or study coordinator must notify the Sponsor within 24 hours if a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1 – Safety Parameters.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the CRF:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death of subject
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the CRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a medical need to withdraw the subject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject from participation in the study
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including telephone calls, letter sent by certified mail or equivalent.
- Other: The subject was terminated for a reason other than those listed above, such as the termination of the study by the Sponsor.

4.3.5 SUPPLEMENTATION OF STUDY SUBJECTS

If more than 10% of subjects from randomization of study treatment discontinue prior to the Week 36 primary endpoint procedures, then supplementation of study subjects will be considered.

5 STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The active and placebo formulations to be used in this study are described in Table 13. Both IPs will presented in clear glass cartridges and will be injected intramuscularly.

VGX-3100 and placebo will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 13. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Placebo	150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 BLINDING

This study is double-blinded with blinding maintained throughout the study by use of identical packaging for both the active product and the placebo. There is no difference in appearance for both the active product and the placebo.

The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is essential for proper clinical management of the subject, as judged by the investigator. It is preferred, but not required, that the investigator first contact the Medical Monitor to discuss options before unblinding the subject's treatment assignment. In case of non-emergency, investigator must contact Medical Monitor to discuss the options before unblinding the subject's treatment assignment.

The Sponsor's or designee's pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE, UADE, or AE of interest. No personnel directly involved with the study will be unblinded. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's treatment assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCT

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, double-panel label with tear-off. Both VGX-3100 and placebo labels will include, at minimum, the following information in Table 14:

Table 14. Example Labels for Investigational Product

Cartridges (primary container)	**Pouches** (secondary packaging)
VGX-3100 or Placebo Insert cap end IM administration Sponsor name	**LABEL BODY** Material ID/Study ID VGX-3100 or Placebo Single-use cartridge containing 1ml IM administration via CELLECTRA® 5PSP Store at 5°C, expiration date Caution Statement Sponsor name and address **LABEL TEAR OFF** Material ID/Study ID VGX-3100 or Placebo Patient ID: _____ Date (DD/MMM/YYYY): _____ Must be used by (time): _____

5.4 HANDLING OF INVESTIGATIONAL PRODUCT

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Unless otherwise specified, IP will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Immediately upon arrival, IPs should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition.

Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

5.5 DISPENSING OF INVESTIGATIONAL PRODUCT

It is the responsibility of the Investigator to ensure that the IP is only dispensed to study subjects. It must be dispensed only from official study sites by authorized personnel according to local regulations.

When a subject is eligible for randomization, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration. The pouch must not be discarded until 1) administration is completed and 2) all pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator.

The device user manual and instructions for use will inform clinical personnel about placement of the IP cartridge into the device, as well as the steps for injection and electroporation.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at site per institution policy or returned to Inovio Pharmaceuticals, Inc. or its designee, if site cannot destroy IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor.

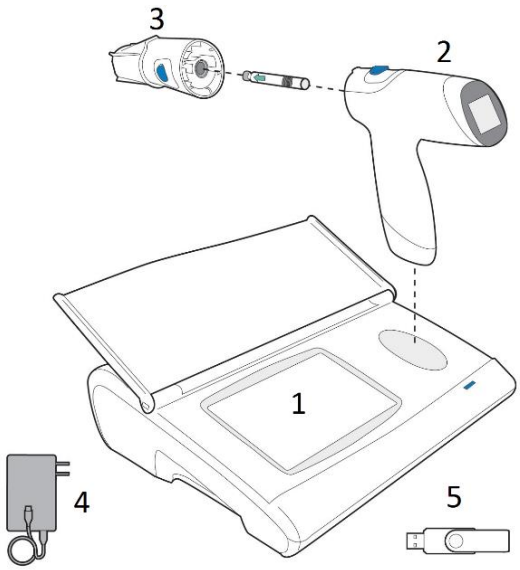
The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

If IP is returned to Inovio Pharmaceuticals, Inc., or its designee, it must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8 CELLECTRA™ 5PSP DEVICE

The Investigational product\placebo will be delivered using the CELLECTRA™ 5PSP device. The device consists of five (5) main components (see Figure 2):

Figure 2: CELLECTRA 5PSP Base Station with Handset



1) The 5PSP Base Station serves as a charging dock for the Handset and can accept limited data inputs as well as store records.

2) The reusable 5PSP Handset is battery powered and delivers the electroporation pulses. The Handset accepts the disposable array.

3) The 5PSP Sterile Single Use Array consists of five (5) needle-electrodes bonded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

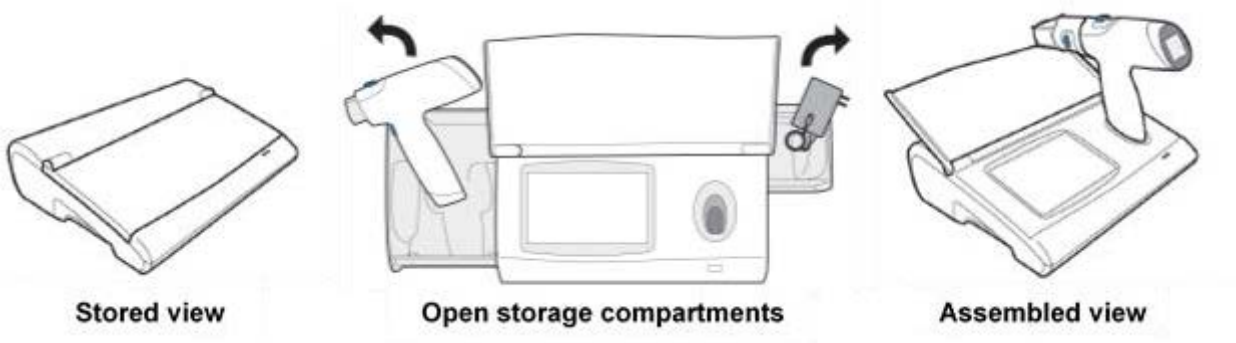
4) USB International Power Supply

5) Flash Drive used to transfer device logging data to the manufacturer.

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset. The base station is illustrated in Figure 3.

Figure 3: CELLECTRA™ 5PSP Base Station



<u>Handset</u>

The handset facilitates delivery of the needles for injection and the electroporation pulses into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the

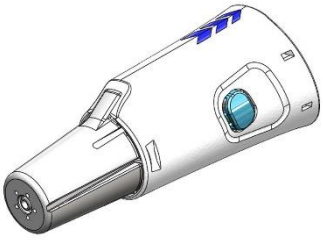
handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire. The handset is illustrated in Figure 4.

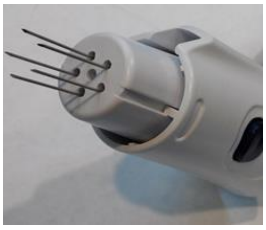
Figure 4: CELLECTRA™ 5PSP Handset

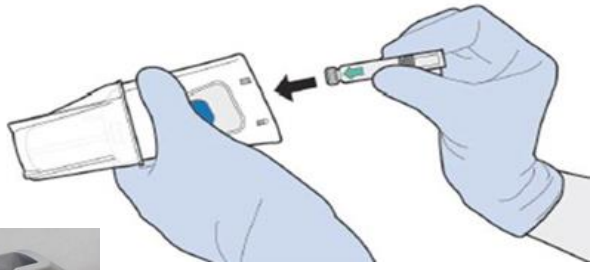
Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 intramuscular injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array (indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The array is illustrated in Figure 5. The array features no software.

Figure 5: CELLECTRA™ 5PSP Array







5.9 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of the device are located in the CELLECTRA™ 5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training. Training will include review of the device user manual as well as hands-on training. After training on the proper use of the CELLECTRA™ 5PSP device, intended users at each site will be required to demonstrate their competence in its use to Inovio or its designee. An instructional video has been prepared for review by site personnel on an as needed basis.

The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel.

Any deviation from the above procedures must be approved by the sponsor or its designee.

5.10 PACKAGING AND LABELING OF CELLECTRA™ 5PSP DEVICE

See below Figure 6 for example CELLECTRA™ 5PSP device component labels.

Figure 6. Device Labels (Base, Handset, Array)

BASE STATION

HANDSET

ARRAY

5.11 HANDLING OF CELLECTRA™ 5PSP DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual.

5.12 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational product. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP serial number, array lot number and the study drug lot number. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.13 RETURN OF CELLECTRA™ 5PSP DEVICES

Upon completion or termination of the study, all devices and unused components must be returned to Inovio Pharmaceuticals, Inc.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by Inovio Pharmaceuticals, Inc. or the responsible Study Monitor.

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions will not be granted with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct.

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who have been identified with standard of care biopsy results of CIN 1/2, CIN 2, CIN 2/3 or CIN 3 and who consent to participate in the study will be eligible for screening and will have biopsy slides or tissue sent to the central pathology lab for review by PAC for evaluation prior to enrollment.

Additionally, Investigators may discuss with the Sponsor on a case-by-case basis the screening of subjects with abnormal cytology findings (i.e. HSIL or ASC-H with or without local HPV-16 or 18 genotype results) obtained as part of standard of care. The specific circumstances MUST be submitted in writing (e.g. email or fax) and the medical monitor MUST be consulted prior to screening a volunteer with these cytology findings (i.e. ASC-H or HSIL with or without HPV-16 or 18) for this study. The initial biopsy results may have been obtained at a referring institution by someone other than the site investigator.

- In the case where the subject has an ASC-H or HSIL cytology result without HPV-16 or 18 genotyping results available locally and if approved by Inovio, the site may proceed with initial study screening by sending ThinPrep™ samples to the central laboratory to screen for HPV 16/18 by cobas™ assay. A non-specific result from local testing of "Positive for high risk HPV" is not sufficient and will require the collection of the ThinPrep™ sample for HPV-16 and/or HPV-18 testing by cobas™ assay. If the central lab ThinPrep™ sample result is positive for HPV-16 and/or HPV-18, the site may continue screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.
- In the case where the subject has an ASC-H or HSIL cytology result with HPV-16 or 18 positive genotype results available locally and if approved by Inovio, the site may proceed with initial study screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.

Subjects who consent to participate will have biopsy slides or paraffin-embedded tissue block(s) from a previous biopsy and/or newly collected cervical biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by PAC. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e.

slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

- Biopsy specimens and colposcopic photographs obtained within 10 weeks prior to Day 0 as part of standard of care before the informed consent may be used as part of the screening and evaluation process. If the pathology results of the initial biopsy obtained as part of standard of care are available confirming the presence of cervical HSIL (CIN2 or CIN3), those biopsy slides or sample(s) may be sent directly to the central pathology lab after the subject has signed the informed consent.

For those individuals diagnosed with cervical HSIL by a local pathologist, where the initial biopsy slides or tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable time frame, colposcopy should be performed and an additional biopsy sample collected during screening. A photograph of the lesion with at least one attempt should done as follows: Acetic acid should first be applied to the cervix then photographs of the cervix and the associated lesion should be photographed prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit.
The 10 week screening window begins upon collection of the biopsy sample that will be evaluated by the PAC.

Subjects must have a histologic diagnosis of cervical HSIL (CIN2 or CIN3) confirmed by the PAC and a screening ThinPrep™ cervical specimen test positive for HPV-16 and/or HPV-18 by cobas™ HPV test to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18. Subjects' post-menopausal status must meet requirements as specified in the inclusion criteria [1, 2]. The assessments during the screening period will determine the subjects' continued eligibility for the study and also their ability to comply with protocol requirements by completing all assessments.

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the safety laboratory collections/assessments, which must be performed within 45 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent
- Demographics; including age, and race/ethnicity
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- Full Physical Examination (including height, weight and BMI measurements)
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)

- Urine pregnancy test
- Colposcopy with lesion photography and/or cervical biopsy (Screening colposcopy and photography is optional if adequate colposcopy was performed upon collection of initial biopsy)
- 12-lead ECG (within 45 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 45 days prior to Day 0);
- Serology (HIV Antibody, within 45 days of Day 0)
- Determination of eligibility per inclusion / exclusion criteria
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluations will be performed on **Day 0 prior to study treatment:**

- Determination of eligibility per inclusion / exclusion criteria
- Randomization
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile (a total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0)
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) sample by oral rinse and vaginal swabs for HPV testing
- Intra-anal swabs (if subject has consented for intra-anal sampling) for HPV testing
- Colposcopy (accompanying lesion photography should be attempted at least once)
- Patient-Reported Outcome (PRO) questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

Study treatment will be administered and the following evaluations will be performed on **Day 0 post-treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)
- Download EP data from device within 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review Day 0 PDC (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.3 WEEK 4

The following study evaluation will be performed on **Week 4 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect PDC for dose 1

The following study evaluations will be performed **on Week 4 post treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.5 WEEK 8

The following study evaluation will be performed during the visit

- Vital signs
- Targeted Physical assessment
- Collect and review PDC for dose 2
- Post treatment adverse event and injection site reaction evaluation

- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Whole blood (at least 34 ml) and serum (at least 8 ml serum) for immunology including miRNA profile

6.2.6 WEEK 12

The following study evaluation will be performed on **Week 12 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test

The following study evaluations will be performed **Week 12 post treatment**:

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.7 8-14 DAYS POST DOSE 3 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 3 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.8 WEEK 15

The following study evaluations will be performed on **Week 15 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Post-treatment injection site reaction assessment
- Urine pregnancy test
- Whole blood (at least 51 mL) and serum (at least 4 mL) for immunology
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be instructed to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Collect PDC

- Colposcopy (lesion photography should be attempted at least once)

6.2.9 WEEK 28

The following study evaluations/actions will be performed on **Week 28 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy (lesion photography should be attempted at least once) to assess for possible disease progression.
- ECC (only to be collected if ECC was done as part of Screening)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 28 visit by a subject enrolled in US, Canada, Mexico, Germany and UK only

6.2.10 WEEK 36

The following study evaluations will be performed on **Week 36 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Socio-Behavioral assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Whole blood (at least 34 ml) and serum (at least 4 ml) for immunology
- Urine pregnancy test
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) by oral rinse and vaginal swab for HPV testing
- Intra-anal swab (if subject has consented to intra-anal sampling) for HPV testing
- Colposcopy (lesion photography should be attempted at least once)
- Biopsy or surgical excision based on information collected at Week 28 to determine the minimally required tissue collection procedure (e.g. 4 quadrant biopsies, 4 quadrant biopsies and ECC, or surgical excision) to be used for histopathologic assessment at Week 36 as described in Tables 5 & 6
- PRO questionnaire (EQ-5D-5L only) completion by a subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.11 WEEK 40 PHONE CALL

The following study evaluations will be performed on **Week 40 ± 2 weeks** via a phone call:

- AE/SAE assessment

- Review of histology results as read by PAC from Week 36
- Completion of quality of life questions will asked to subjects enrolled in US, Canada, Mexico, Germany and UK only
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 40 by a subject by subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.12 WEEK 62

The following study evaluations will be performed on **Week 62 ± 2 weeks:**

- Targeted physical assessment
- Vital Signs
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy (lesion photography should be attempted at least once)

6.2.13 WEEK 88

The following study evaluations will be performed on **Week 88 ± 2 weeks:**

- Full Physical Exam
- Vital Signs
- Socio-Behavioral Assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Urine pregnancy test
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) by oral rinse and vaginal swabs for HPV testing
- Colposcopy (lesion photography should be attempted at least once)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the

subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with [redacted] (e.g., [redacted]). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.3 SAFETY EVALUATIONS

6.3.3.1 Physical Exam

A full physical examination (PE) will be conducted during screening and study discharge. It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

A targeted physical assessment will be performed at other visits as determined by the investigator or directed per subject complaints.

6.3.3.2 Vital Signs

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 Weight and Height

Weight and height will be collected at screening in order to calculate the BMI. Weight will be collected on Day 0, Weeks 4 and 12.

6.3.3.4 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. The medical history will include a) any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s), and b) if treated previously for CIN, the respective treatment type(s) and date(s).

6.3.3.5 Socio-Behavioral Assessment

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 36 and 88, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 Laboratory Evaluations

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- Serum glutamic-pyruvic transaminase (SGPT)/Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose $\geq$ 1+) a microscopic examination should be performed.

6.3.3.7 Demographics

Demographic information will be collected via self-report (unless noted otherwise), including the following:

- Age
- Race/ethnicity

6.3.3.8 Urine Pregnancy Testing

For subjects of reproductive potential, a negative spot urine pregnancy test is required prior to each study treatment, colposcopy and surgical excision.

6.3.3.9 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QTcb or QTcf, ST segment, T wave as well as an investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as "clinically significant (CS)" or "not clinically significant (NCS)" by the investigator.

6.3.3.10 Subject Self Evaluation

Subjects will be provided a PDC and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PDC will be reviewed with the subject by the study staff at 8 -14 days post-dose phone call and next in-person visit.

The study staff will review the PDC for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications.

Any PDC entry determined to meet the CTCAE criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. If the PDC entry does not meet the criteria of a Grade 1 or higher AE as per the CTCAE guidelines, clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the PDC entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a 3-dose series of either 1 ml VGX-3100 or Placebo by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with the CELLECTRA™ 5PSP. Study treatment must not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.4.1 RISKS OF TREATMENT PROCEDURES

A summary of the potential risks of IM administration followed by EP with the CELLECTRA™ 5PSP can be found in the VGX-3100 Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO TREATMENT

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at Day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

Medication taken for anxiety or pain management should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening will be performed for inclusion into the study as listed in section 6.1.1.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and at least 30 minutes after each study treatment and at 2 to 4 weeks post study treatment visits. They will also be advised to record local and systemic AEs for 7 days on a PDC.

An adverse event assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 15. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, two previously-validated patient-reported outcomes (PRO) instruments will be provided to the subjects enrolled in US, Canada, Mexico, UK and Germany. The following two PRO questionnaires will be used:

1. Short Form Health Survey, **version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [26]
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [27, 28]

Either one or both PRO instruments (refer to Section 6.2) will be provided to the subject who will be instructed to complete the questionnaire at the following time points:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- Week 4 (after study treatment)
- 8-14 days post dose 2
- Week 12 (after study treatment)

- 8-14 days post dose 3
- 8 -14 days post Week 28
- Week 36 (after biopsy or surgical excision)
- 8-14 days post Week 40
- Week 88

Administration of PRO instruments will be performed according to the validated procedure and guidelines of each respective instrument, except for some assessments for exploratory analyses. Additional instructions will be provided separately.

Additional questions related to the subject's quality of life following surgery or biopsy will be completed at the Week 40 phone call for subjects enrolled in USA, Canada, Mexico, UK and Germany.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 8, 15, and 36.

Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine 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). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 as well as Week 8. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 8 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

Profiling of DNA methylation status will occur via the use of nucleic acid isolated from Digene brushes used at Screening, Day 0 and Week 15. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in DNA

methylation profiles that occur once dosing with VGX-3100 has finished to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immune assessment. Available tissue collected from pre- and post- treatment may be assessed for the presence of immune cells using immunohistochemistry or immunofluorescence. The presence of immune signatures may also be analyzed through the assessment of various transcripts suggestive of an inflammatory or an immunosuppressive tissue microenvironment.

An Immunoscore algorithm will be applied to cervical tissue obtained at baseline. The algorithm is composed of scoring patients based on infiltration of immune cells stained with CD8, FoxP3, CD103 and Perforin. Scoring will occur in epithelium designated as HSIL.

For HSIL epithelium, 1 point will be assigned for patients who show at least two of the following three parameters:

- CD8 count per mm^2 >375,
- perforin count per per mm^2 >0 and
- CD103 count per per mm^2 >150

Additionally, 1 point will be assigned for each for the following parameters:

- FoxP3/CD8 ratio <1:3,
- CD103/CD8 ratio >2:1,
- CD103/ perforin ratio >10:1 and
- CD103/FoxP3 ration > 1.5:1

6.11 HLA TYPING

HLA testing will be performed on PBMC from any single blood sample collected for immunogenicity analysis. If the subject has a record of previous high resolution HLA testing and access to the results, then HLA testing is not required.

The DNA extracted from the blood sample will be used to determine if alleles at the MHC locus affect the immune response to study treatment. Data arising from this analysis will be subject to the same confidentiality restrictions as the rest of the study. This specimens will be destroyed after the analysis is completed.

6.12 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at the screening, Day 0, Weeks 8, 15, 28, 36, 62, 88 and read in a central laboratory. HPV PCR by cobas™ HPV test will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer at Day 0, Weeks 15, 28 or 36, the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples to eliminate potential interference with the results of HPV testing.

At visits (i.e. Screening, Day 0, and Weeks 15, 28, 36 and 88) where multiple cervical samples are collected, the two Digene cervical swab will be collected prior to the ThinPrep™ sample. Immunology testing may be performed from Digene swab.

Details of sample collection and shipment information will be provided in the laboratory manual.

Additionally, if there is residual tissue available from cervical tissue from screening and Week 36 after the histologic diagnosis have been rendered, then unstained slides and/or paraffin blocks may be collected to test for HPV typing.

Also, non-cervical swabs (i.e. oropharyngeal rinse, vaginal brush and intra-anal swabs) will be collected at specified visits for HPV typing.

6.13 COLPOSCOPY AND CERVICAL BIOPSIES

Colposcopy at screening must be adequate, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected dysplasia. An ECC is not required for study entry. However, if an ECC was done as part of routine care during the screening period, and found to have evidence of cervical HSIL such subject should not be enrolled in the study. Colposcopy is not required to be performed at screening if adequate colposcopy was previously obtained upon collection of initial biopsy. All colposcopies performed after informed consent should be conducted according to the guidelines outlined in Appendix A.

Interval colposcopies will be performed at Day 0, Weeks 15, 28, 36, 62, and 88. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

At least one attempt to photograph the lesion should done as follows: Acetic acid should first be applied to the cervix then photograph(s) of the cervix and the associated lesion should be taken prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit. Pictures should be taken to obtain a quality image to the extent feasible according to investigator judgment.

If a biopsy or surgical excision is performed, images of the cervix should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach and 2) the process for uploading the images to a secure server. Additionally, if a vaginal or vulvar lesion should develop after a subject is enrolled, photographs should also be taken to document the clinical exam finding.

6.13.1 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at screening to confirm eligibility. If the criteria outlined in Table 5 or 6 are met, ectocervical biopsies may also be performed at Week 36 to provide tissue for histopathologic assessment of disease regression.

Visualization of a normal appearing cervix by colposcopy is insufficient evidence to confirm disease regression at Week 36. Biopsy must be performed at the location of the screening biopsy if no disease is visible at Week 36.

Biopsies should not be performed at any other visit unless there is suspicion of disease progression. Removal of additional tissue by biopsy before Week 36 will bias results toward improvement regardless of whether the subject is in the active or placebo group. The bias introduced will obviously be more significant for smaller lesions. For this reason, if biopsies are obtained prior to Week 36, the subject will be classified as a non-regressor in the efficacy analyses. Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy prior to Week 36, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.13.2 UNSCHEDULED BIOPSIES

In the event an unscheduled biopsy is performed prior to Week 36, the subject will be classified as a non-responder. The subject will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and the Investigator's judgment based on the results of the histological diagnosis from the unscheduled biopsy Additional instructions for collecting ectocervical biopsies are detailed in Appendix A. All biopsy samples/excised tissue will be sent to the central pathology lab for review by PAC.

6.14 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to the screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.15 RESTRICTIONS

6.15.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled otic and ophthalmic corticosteroids are allowed
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine

- Blood thinners (e.g. anticoagulants, antiplatelet drugs) or other medication that affects blood clotting within 2 to 14 days (e.g., 4-5 drug half-lives) of any study treatment, biopsy or excisional procedure (e.g. LEEP)

6.15.2 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal death, still birth, congenital anomaly of the fetus/newborn); see Section 7.1.9 for additional information on pregnancy reporting.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.2.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.

- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.
Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.

7.1.2.2 Event Reporting for Disease Progression or Exclusionary Histologic Findings Post-study Treatment

After starting study treatment, if there is histologic confirmation of progression of cervical HSIL to micro invasive or invasive squamous cell carcinoma, the event must be reported as an SAE. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances, the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.3 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable

regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.4 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

For countries recognizing and regulating CE Mark devices, SAEs related only to the device which meet the medical device vigilance (MDV) reporting criteria will be handled by the Sponsor under the post-market surveillance/vigilance reporting requirements per MEDDEV 2.12-1. In such cases, the Sponsor will report as per the regulations to the relevant health authorities that require MDV reporting.

7.1.5 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported.

The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life Threatening)
- Grade 5 (e.g. Death)

The investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.6 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the CELLECTRA™ 5PSP device. An AE may also be assessed as not related to the IP and/or the device. Because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the device indicating "yes" or "no" accordingly. Causality should be assessed by the investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event.

7.1.7 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

7.1.8 POST-STUDY REPORTING REQUIREMENTS

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.9 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to Week 36 will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor or its designee within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax, as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject.

All pregnancies that occur from the time of first screening procedure through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF THE COLLECTION AND RECORDING OF SAFETY DATA

Non-serious AEs and SAEs (and UADEs) will be collected for each subject from the time when informed consent is obtained through Week 88.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).

2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE (or UADE) occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
-
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100/placebo delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

- Grade 3 or greater persistent administration site erythema, and/or induration recorded ≥ 2 hours immediately after Study Treatment
- Grade 4 or greater persistent administration site pain, tenderness recorded ≥ 2 hours immediately after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

Sites will inform the Sponsor via method described in section 7.4.1 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

- If at any time during a study one-third (1/3) or more of the subjects experience an AESI, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB. Only the DSMB may review unblinded data in making their recommendation to the Sponsor regarding continuation of a trial.

- If any SAE (or potentially life-threatening AE), or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

- If three or more subjects in this study, experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

The sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

7.4 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the AE CRF.

7.4.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) (see Section 7.3.1) require expedited communication from the Site to the Sponsor. Within 24 hours of the site's awareness of the event, AESI must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the investigator must notify the Sponsor via email or phone.

AESI reporting if EDC system is unavailable

EMAIL: [redacted]
SAFETY PHONE: [redacted]

7.4.2 STUDY REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure.

An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.3 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.4 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter

notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to the Sponsor or the appropriate designee.

Within 24 hours of the site's awareness of the event, all SAEs (regardless of relationship to investigational product) must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the paper SAE Report form should be used and faxed to the PPD Pharmacovigilance (PVG) Safety Hotline Fax Number shown below:

Facsimile (FAX) reporting if required[a]:

Americas FAX#: [redacted]
Europe FAX#: [redacted]

a: Reporting by FAX is required for paper SAE Report Forms if electronic data capture (EDC) is not available, redacted supporting medical records, and Pregnancy Report Forms.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor. The supporting documents for SAE reports should be sent by fax to the PPD PVG Safety Hotline Fax Number, shown above.

Investigator will supply the Sponsor and the IRB with more information as it becomes available and any additional requested information. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical

investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.3 and 7.1.4).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor with 10 days of discovery. Any product complaint that involves an AE or SAE must be also reported per Section 7.4.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation.

Additional instructions on reporting to be provided separately.

7.5 STUDY DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8 STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects with a histologic diagnosis of cervical HSIL. The study's primary endpoint is binary: regression to CIN1/normal and clearance of HPV-16 and/or HPV-18 infection, based on tissue collected at Week 36. The primary hypothesis is that VGX-3100 will be superior to placebo regarding the proportion who achieve the primary endpoint. Secondary efficacy analyses involve regression to CIN1/normal, clearance of HPV-16 and/or HPV-18 infection from cervical tissue and non-progression of cervical lesions. Other secondary analyses concern safety and humoral and cellular immunological measures, and association of Immunoscores and efficacy. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, virology, other microRNA (miRNA) profiles, and DNA methylation profile and efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized (2 VGX-3100:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) BMI category ($\leq$25 vs. >25 kg/m^2), and c) age category (<25 years vs. $\geq$25 years). There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

The study is double-blinded.

8.3 SAMPLE SIZE/POWER

A sample of 198 subjects will be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 35% and 14% for VGX-3100 and placebo, respectively. These proportions also incorporate missing data (~10%) classified as non-regressors (failures). The assumptions are based on the Phase 2 study results.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The intention to treat (ITT) population includes all subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be primary for the analysis of efficacy in this study.
- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding ITT population for the analysis of efficacy.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding ITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date; start dates will not be imputed. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true population probabilities of the primary endpoint for VGX-3100 and Placebo, respectively. The primary hypothesis of superiority is:

$$H_0: \delta \leq 0 \textit{ vs. } H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [29]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

The secondary efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. It also includes subjects who undergo early intervention prior to this time frame or subjects who have no endpoint data for this time frame; these subjects are considered as failures for the efficacy endpoints. Table 7 through Table 11 provide details for the definition of the endpoint responses.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and also the secondary efficacy endpoints of regression and clearance individually and the Immunoscore results. Relationships will be examined by using logistic regression models which model the efficacy outcomes versus the Immunoscore results and treatment group as regressor variables.

An exploratory analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) DNA methylation results, d) colposcopy results, e) cytology results, and f) HPV results. Relationships will be examined by using logistic regression models which model the primary endpoint outcome versus these results and treatment group as regressor variables.

Other exploratory analyses will examine durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue at Weeks 62 and 88. Descriptive statistics will be utilized; percentages of subjects who cleared will be presented by time point or anatomic location and treatment group.

8.10 IMMUNOGENICITY ANALYSES

Post-baseline cellular and humoral responses will be compared between treatment groups using a difference in medians and associated exact non-parametric 95% CI. Increases from baseline in interferon-γ ELISpot response magnitudes and in CD8+ / CD137+ PBMCs Perforin+ results and HPV E6 and E7 titers from ELISA at Weeks 8, 15 and 36 visits will be evaluated.

Post-baseline tissue response magnitude will be compared between treatment groups using a difference in means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

The mITT population will be used for immunogenicity analyses.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 28 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [29]. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

For AE data, partial start dates will be imputed to the date of treatment to conservatively report the event as treatment-emergent, whenever the portion of the date is consistent with that of the study treatment. Otherwise, it will be imputed to the earliest date consistent with the partial date. A completely missing onset date will be imputed as the day of treatment. Partial stop dates will be assumed to be the latest possible day consistent with the partial date.

AE duration will be calculated as (Stop Date – Start Date) + 1.

8.11.2 LABORATORY DATA

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be

summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

8.12 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

8.13 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the ITT population.

8.14 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes among subjects who receive VGX-3100 will be compared between those with excision versus those without excision, based on PRO endpoints. This comparison will utilize the median endpoint or the proportion of subjects with endpoints and associated Wilcoxon rank-sum test or Pearson chi-square test/Fisher's exact test, for continuous responses and categorical responses, respectively.

The mITT population will be used for PRO analyses.

8.15 MISSING VALUES

Missing data will be considered as non-regressors (failures) for the ITT efficacy analysis. A subject's regression outcome is missing if her CIN grade and HPV clearance at Week 36 cannot be determined. Also, any subject who undergoes an unscheduled procedure in which cervical tissue sample was obtained before Week 36 will be considered a non-regressor regardless of the Week 36 result. Efficacy analyses using the mITT population will be conducted and will serve as sensitivity analyses regarding missing data.

8.16 SUBGROUP ANALYSES

Primary and secondary efficacy endpoints will be analyzed by history of exposure to prophylactic HPV vaccines.

8.17 INTERIM ANALYSIS

No formal interim analyses will be performed for this study. For reasons of futility (early evidence of poor efficacy of VGX-3100) or safety issues, the DSMB could recommend stopping enrollment at any time. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

9 DATA COLLECTION, MONITORING AND REPORTING

9.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed

to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

9.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. This retention period may be superseded by applicable regulatory requirements (e.g. minimum of 25 years for Health Canada). The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.4 SAFETY AND QUALITY MONITORING

9.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The DSMB charter will define the membership, responsibilities and procedures for the meeting.

9.4.2 PATHOLOGY ADJUCATION COMMITTEE

All histology slides (i.e. cervical biopsies or surgical excision tissue) will be read by a Pathology Adjudication Committee (PAC) to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion.

9.4.3 CLINICAL MONITORING

Clinical Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies

- Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
- Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
- Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the study facilities continue to be acceptable
- Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

10 ETHICS

10.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2 INSTITUTIONAL REVIEW BOARD OR INSTITUTIONAL ETHICS COMMITTEE (IRB/IEC)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/IEC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/IEC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/IEC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

10.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

11 PROTECTION OF HUMAN SUBJECTS

11.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

11.2 COMPLIANCE WITH IRB/IEC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator must be provided to Sponsor.

11.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

11.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

11.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Product used in this study however will be asked to complete a participant diary card during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

11.6 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the sponsor in all participating countries and is fully supporting the study. Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted.

13 PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

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15 APPENDIX

15.1 APPENDIX A: GUIDELINES FOR COLPOSCOPY, BIOPSY, AND SURGICAL EXCISION

Colposcopy Procedure

It is recommended that all study colposcopies performed after informed consent be according the procedures recommended by the American Society of Colposcopy and Cervical Pathology (ASCCP):

1. Use warm, clean water to lubricate the vaginal speculum. Avoid other lubricant substances which could obscure results.
2. If the vaginal walls are lax, a lateral vaginal sidewall retractor aligned perpendicular to the speculum may facilitate visualization.
3. Examine the cervico-vaginal secretions and remove any excess mucus from the cervix with saline-soaked cotton swabs.
4. Obtain any required specimens required for cytology and HPV testing.
5. Using low-power magnification (5x to 10 x) inspect the cervix for obvious areas of abnormalities.
6. Swab or spray the cervix with 3-5% acetic acid. Reapply every 2-3 minutes during the examination.
7. Use the green or blue filter to examine blood vessels. Increase magnification (15x)
8. Identify the distal and proximal boarders of the transformation zone.
    a. The inner border is the entire 360-degree circumference of the squamocolumnar junction
        i. If the junction is proximal to the external os, in the canal, use a cotton-tipped applicator to pry either the anterior lip up or the posterior lip down or use an endocervical speculum
        ii. If the junction is not visualized in its entire circumference, the colposcopy is deemed inadequate
    b. The distal limit of the transformation zone may be identified by finding the most distal crypt openings or nabothian follicles in the lips of the cervix and drawing an imaginary line connecting these landmarks
9. Inspect the entire new squamocolumnar junction and detect and evaluate any abnormal areas.
10. Evaluate the upper third portion of the vagina.
11. Lugol or Schiller's solution may be applied to further define previously identified lesions.

Cervical Biopsies

Endocervical Curettage

ECC is to be performed using a kervorkian curette or equivalent instrument. Rotate and scrape the curette 360° in the endocervical canal and use a cytobrush to remove the specimen. Deposit the specimen onto a Telfa pad before depositing in the specimen vial containing 10% neutral buffered formalin solution and labeled with the subject identification (SID) number.

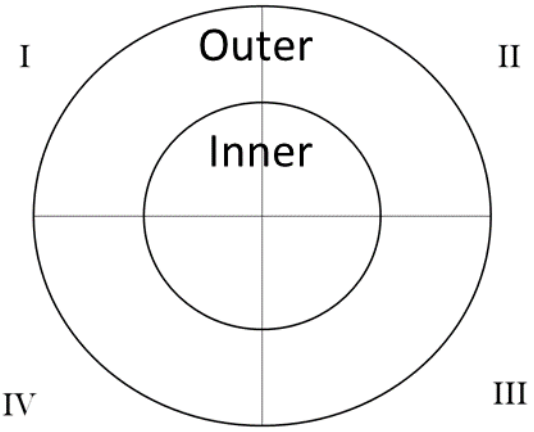
Ectocervical Biopsies

Ectocervical biopsies should only be performed prior to Week 36 if disease progression is suspected. Only the suspect lesion should be biopsied in that circumstance.

If the subject is eligible for 4 quadrant biopsy at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the subject's ID number and the quadrant number according to the figure below.
2. Perform and record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform colposcopic directed biopsies from all quadrants with lesions.
4. Multiple biopsies can be obtained of a lesion at the discretion of the investigator but must be uniquely labeled
5. If a quadrant is free of lesions, obtain a random biopsy at the squamocolumnar junction in that quadrant at 2, 4, 8, or 10 o'clock.
6. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Figure 1 – Biopsy Quadrant Numbers



Surgical Excision

For subjects undergoing surgical excision at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the SID number and the specimen type.
2. Record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform the LEEP or CKC per usual practice.
4. Specimen should be marked at 12 o'clock with suture or gentian violet ink for purposes of orientation
5. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Protocol Approval Page

HPV-301
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

Protocol Version: 4.0
Protocol Version Date: 29Mar2018

Written by:

[redacted] Date (ddMmmyyyy)

Reviewed and Approved by (Director or above):

[redacted], MD, PhD
Medical Monitor
Date (ddMmmyyyy)

[redacted]
Date (ddMmmyyyy)

[redacted]
Date (ddMmmyyyy)

[redacted]
Date (ddMmmyyyy)

[redacted]
Date (ddMmmyyyy)

Protocol Approval Page

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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

Protocol Version: 4.0
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Written by:

[redacted] Date (ddMmmyyyy)

Reviewed and Approved by (Director or above):

[redacted], MD, PhD [redacted] Date (ddMmmyyyy)
Medical Monitor
[redacted]

[redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

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Medical Monitor
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[redacted] Date (ddMmmyyyy)

[redacted] [redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

HPV-301

REVEAL 1 Trial

(Randomized Evaluation of VGX-3100 and Electroporation for the Treatment of Cervical HSIL)

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

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

EudraCT #2016-002761-63

Version 5.0

20 November 2019

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

Short Title: REVEAL 1 Trial (Randomized Evaluation of VGX-3100 and Electroporation for the treatment of Cervical HSIL)

Biological Product: VGX-3100

Protocol Number: HPV-301

Sponsor: Inovio Pharmaceuticals, Inc.
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Inovio Pharmaceuticals, Inc.

SUMMARY OF CHANGES

The following is a list of protocol changes in order of appearance from HPV-301 protocol version 4.0 dated 29 March 2018 to HPV-301 protocol version 5.0 dated 13-Jun-2019, after which administrative clarifications are listed.

1. HLA testing and associated exploratory endpoint #2 has been removed from the protocol in consideration of the HPV-003 results which showed no clear association of HLA background as a predictor of response.
2. Group-level unblinded (VGX-3100, Placebo) summaries and analyses of efficacy will be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. Long-term follow-up data will continue to be collected for all subjects with remaining visits through the final Week 88 visit. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and all other efficacy endpoints corresponding to the cervix and the Week 36 visit on which to make decisions regarding the VGX-3100 program, while still gathering secondary and exploratory endpoint and safety data through the final Week 88 visit. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance, b) the secondary endpoint of histopathologic regression, c) the secondary endpoint of virologic clearance, d) the secondary composite endpoint of histopathologic regression to normal and virologic clearance, e) the secondary endpoint of histopathologic regression to normal, and f) the secondary endpoint of histopathologic non-progression. None of these summaries or analyses will be provided if the total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group relative to this total count is less than 3% for a given summary/analysis. Also, items a) through f) are planned to be produced in the order in which they are listed, but as there are intersecting endpoints among these items, items among b) through f) will not be produced if the difference in total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group is 0, relative to any preceding item in the set. The group-level unblinded (VGX-3100, Placebo) production of the summaries and analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), PPD, which has already been providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded with respect to subject treatment assignment throughout the trial.
3. The stopping rules outlined in Section 7.3.2, Stopping Rules (Criteria for Pausing of Study), have been clarified to focus on unexpected verified events and not include events that are already described as known adverse drug reactions.

Administrative Changes:

1. Text was included to clarify that the calculation of Body Mass Index (BMI) used to determine the stratification group at randomization should be performed using the Day 0 measurements.

2. Text was included to clarify that the designation of age category (<25 years vs. ≥25 years) used to determine the stratification group at randomization should be performed using the age at Day 0.
3. An inconsistency in the text in Exclusion Criteria #8a was corrected to clarify that HIV testing should be performed within 45 days prior to Day 0. This change will make the text in the exclusion criteria consistent with the text in Section 6.1.1, Screening Evaluations, of the protocol.
4. A statement was added to Section 1.1.3, Electroporation, for informational purposes indicating that CELLECTRA™ 5PSP device is CE Marked in the European Union.
5. References to table numbers for Tables 4 and 5: Minimally Required Procedures at Week 36 were corrected throughout the document.
6. In Section 2.1.3, the definition of non-responder has been clarified to indicate that subjects who undergo excision or whose cervix are biopsied at any time between their initial dose of study drug and the Week 36 endpoint tissue collection would be considered non-responders, because the point of initial dose represents the start of therapy, in contrast to the screening period. Also confirming ECC alone is not included under these circumstances.
7. The timing of the virology clearance sample has been clarified to include samples taken on the same date as tissue removal, as time of tissue removal is not captured.
8. Text regarding return of devices has been updated in Section 5.13, CELLECTRA™ 5PSP Device, to clarify that devices and device components may be returned to Inovio, which allows the possibility of destruction of device components on site or carry over of supplies for another study, where appropriate.
9. Digene sample collection has been removed from Week 88 Visit as there is no endpoint associated to this sample at this time point.
10. Table 15 was updated to clarify prevents daily activity. The timeframe for daily activity refers to an impact lasting ≥ 24 hours.
11. The pregnancy reporting timeframe for those participants that become pregnant while participating in the trial that is outlined in Section 7.1.9, Procedures for Documenting Pregnancy During Study, was corrected to reflect that pregnancies will begin being collected starting from first study treatment instead of first screening procedure. Beginning collection of pregnancies during screening would require the Investigator to follow pregnancies even for subjects that are not eligible for the study and are considered screen failures. It is not the Sponsor's intent to collect information regarding pregnancy outcome for subjects that are not exposed to Investigational Product.
12. Administrative clarifications were made to Section 8, Statistical Analysis Plan, as follows:
    a. Section 8.1: correction that the association of Immunoscores and efficacy is an exploratory and not a secondary objective.

b. Section 8.10: correction that immunogenicity assessments will be conducted post-baseline at Weeks 15 and 36. Week 8 was removed for consistency with other protocol sections.

c. Section 8.11.2: because there are no safety laboratory post-baseline measurements, this section that pertained to changes from baseline is not applicable and was removed.

d. Section 8.14: further clarity and specification was included regarding the planned PRO analyses.

13. Clarification was made to Section 15, Appendix A: Guidelines for Colposcopy, Biopsy, and Surgical Excision. Study participants qualifying for 4 quadrant biopsies should have biopsies collected from all four quadrants regardless of visible lesion being present.

14. Additional minor grammatical changes have been made for improvement of general readability.

INVESTIGATOR ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Investigator below constitute his/her approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, ICH-GCP guidelines, local legal and regulatory requirements as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____

Investigator – Signature Date (DD/MMM/YYYY)

_____

Investigator – Printed Name

Site Number: _____

Site Name: _____

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I LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
Baseline	Prior to first dose
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CMI	Cell mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
DNAme	Methylated Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation with CELLECTRA™ 5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LSIL	Low grade squamous intraepithelial lesion
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
miRNA	Micro Ribonucleic Acid
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

II CLINICAL PROTOCOL SYNOPSIS

Title of Study: 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)[1] of the Cervix	
Estimated Number of Study Centers and Countries/Regions: Approximately 125 Sites in up to 25 Countries	
Study Phase: 3	
Primary Hypothesis: Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed HSIL[Cervical Intraepithelial Neoplasia (CIN)2, CIN3] of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit[2]	
Study Drug Dose	6 mg (1 ml)
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device
Schedule	Day 0, Week 4, and Week 12 study visits
No. of Subjects	Approximately 198 subjects will be randomized in a 2:1 ratio to receive VGX-3100 or placebo
Study Duration	88 weeks
Primary Objective	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**
Primary Endpoint	Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsy or excisional treatment) and **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit

[1] Terminology based on 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP)
[2] The time frame is defined as any time starting from 14 days prior to the protocol-specified target date of Week 36

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of all adverse events including Serious adverse events (SAEs) (e.g. Suspected unexpected serious adverse reaction (SUSAR), Unexpected adverse device effect (UADE) and other unexpected AEs) for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by **virologic clearance of HPV-16 and/or HPV-18**	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18 in cervical samples** by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by **complete histopathologic regression of cervical HSIL to normal**	4. Proportion of subjects with **no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both **complete histopathologic regression of cervical HSIL to normal and virologic clearance** of HPV-16 and/or HPV-18	5. Proportion of subjects with **no evidence of LSIL or HSIL** (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) **and no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Week 36 visit
6.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic non-progression**	6. Proportion of subjects with **no progression of cervical HSIL** to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response to VGX-3100 compared with placebo at post dose 3 and Week 36 visits as assessed relative to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15 and 36 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15 and 36 visits

	8c. Flow Cytometry response magnitudes at baseline and Week 15 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe association of microRNA (miRNA) profiles, DNA methylation profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	2. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits), miRNA profile (baseline, Week 8) and DNA methylation profile (baseline, Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Describe the durability of **virologic clearance of HPV-16 and/or HPV-18** for subjects treated with VGX-3100 compared with those treated with placebo	3. Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** by type specific HPV testing at Weeks 62 and 88 visits
4. Describe the patient-reported outcomes for subjects treated with VGX-3100	4. Patient-reported outcome questionnaires self-administered at baseline, after each dose at Weeks 4, 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK
5. Describe the association of a tissue-based score derived using immunologic markers (Immunoscore) at baseline to histological and virological response to VGX-3100 at Week 36	5. Immunoscore results for VGX-3100 treated subjects in conjunction with histological and virological outcomes at Week 36

Study Design:

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled Phase 3 study to determine the efficacy safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16 and/or HPV-18 (HPV-16/18). The composite primary endpoint is histologic regression of cervical HSIL, and clearance of the underlying HPV-16/18 infection. A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true

proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

To be eligible for the study, women age 18 years and above must consent to participate and have biopsy/biopsies of the cervical lesion(s) at the time of screening. The biopsy slides are sent to a central pathology lab for Pathology Adjudication Committee (PAC) review in a blinded manner to establish the presence of cervical HSIL (CIN2, CIN3) prior to randomization. Subjects must also have a cervical ThinPrep™ specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

All eligible subjects will receive three doses of VGX-3100 or placebo administered IM followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment is administered on Day 0, the second at Week 4, and the third (final) study treatment is administered at Week 12. The first dose is administered as soon as possible following confirmation of the cervical HSIL diagnosis and cervical sample positive for HPV-16/18 but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC during screening.

Subjects are randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2) on Day 0, and (c) age category (<25 years vs. ≥25 years) on Day 0. To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

The long term follow up plan following the Week 36 efficacy assessment will include safety, cytology and HPV testing for a period of approximately 1 year (Week 88).

Efficacy: Visualization of a normal appearing cervix by colposcopy and cytology are insufficient evidence to confirm disease regression. Therefore, disease regression will be based on histopathological assessment, which is considered the definitive method for diagnosis. Subjects will also be assessed by colposcopy, cytology, and HPV testing at screening, and at specified visits on and after Day 0. Digital photographs of the cervix following application of acetic acid will also be used to document colposcopic exam findings.

Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (e.g. loop electrosurgical excision procedure (LEEP), large loop excision of transformation zone (LLETZ), cold knife conization (CKC)) or by biopsy (4 Quadrant Biopsy or 4 Quadrant Biopsy with Endocervical Curettage (ECC)) based upon the assessment at Week 28 of cytology, High Risk (HR) HPV status, and colposcopic findings (see Tables 4 and 5, for Minimally Required Procedures).

Safety: All subjects will be followed for 88 weeks.

Subjects will be monitored for:

1) Local and systemic events for 7 days following each investigational treatment as noted on a Participant Diary Card (PDC);
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

Data and Safety Monitoring Board (DSMB): The DSMB will meet quarterly to review unblinded safety data and histopathologic regression results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with histopathologic regression in the VGX-3100 group is unacceptably low compared to the placebo group; no formal interim analysis will be performed for this purpose.

Immunogenicity: Humoral and cell mediated immune responses in response to VGX-3100 treatment will be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15 and 36. Cervical tissue samples will also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

Virology: Cervical cytology samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 8, 15, 28, 36, 62, and 88 by cobas™ HPV test. Additionally, if there is residual tissue in the paraffin block from cervical tissue after histologic diagnoses have been rendered at screening and Week 36, then unstained slides and/or the relevant paraffin blocks may be tested for the presence of HPV-16/18. Vaginal brush and oropharyngeal rinse samples will be obtained at Day 0 (prior to dosing), Weeks 36 and 88 while intra-anal samples will be obtained on Day 0 (prior to dosing) and Week 36 to characterize HPV infection.

Group-level Unblinding: Group-level unblinded (VGX-3100, Placebo) summaries and analyses of efficacy will be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. Long-term follow-up data will continue to be collected for all subjects with remaining visits through the final Week 88 visit. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and all other efficacy endpoints corresponding to the cervix and the Week 36 visit on which to make decisions regarding the VGX-3100 program, while still gathering secondary and exploratory endpoint and safety data through the final Week 88 visit. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance, b) the secondary endpoint of histopathologic regression, c) the secondary endpoint of virologic clearance, d) the secondary composite endpoint of histopathologic regression to normal and virologic clearance, e) the secondary endpoint of histopathologic regression to normal, and f) the secondary endpoint of histopathologic non-progression. None of these summaries or analyses will be provided if the total count of subjects who experience the event of interest is greater than 0 and the count any treatment group relative to this total count is less than 3% for a given summary/analysis. Also, items a) through f) are planned to be produced in the order in which they are listed, but as there are intersecting endpoints among these items, items among b) through f) will not be produced if the difference in total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group is 0, relative to any preceding item in the set. The group-level unblinded (VGX-3100, Placebo) production of the summaries and analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), PPD, which has already been providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded with respect to subject treatment assignment throughout the trial.

Study Population

Inclusion Criteria:

1. Women aged 18 years and above and meets the minimum age of consent per local regulations;
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas™ HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Post-menopausal as defined by spontaneous amenorrhea for more than 12 months;
    b) Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable :
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;
11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

Exclusion Criteria:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;

3. ECC that shows a potentially untreated carcinoma, untreated HSIL, indeterminate, or insufficient for diagnosis (ECC is not required to be performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant through Week 36 visit;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Silgard™, Cervarix™);
7. Presence of any unresolved abnormal clinical screening laboratory values of Grade 1 or greater per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 and deemed clinically significant by the investigator within 45 days prior to Day 0;
8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 45 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results
    g) Subjects who are malnourished (i.e. medically significant unintentional weight loss, kwashiorkor, or marasmus) based on screening labs, medical history and physical exam per the investigator's clinical judgment.
9. Receipt of any non-study, non-live vaccine within 2 weeks of dosing;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of dosing;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
12. Malignancy or systemic treatment for malignancy within 2 years of screening (with the exception of curatively treated, localized anogenital cancers and superficial skin cancers which are permitted)
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;

16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Table 1. Schedule of Events

Tests	Screening (-10 weeks to -1 Day from Date of Biopsy)	Weeks												
		Day 0	8-14 days post Day 0 Phone Call	4 (± 4 days)	8-14 days post Week 4 Phone Call	8 (± 4 days)	12 (± 4 days)	8-14 days post Week 12	15 (± 1 week)	28 (± 1 week)	36 (± 1 week)	40 (± 2 weeks) Phone call	62 (± 2 weeks)	88 (± 2 weeks)
Informed consent	X													
Medical History	X													
Demographics	X													
Socio-behavioral[a]	X										X			X
Inclusion / Exclusion	X	X												
Randomization		X												
Physical exam/assessment[b]	X	X		X		X	X		X	X	X		X	X
Vital signs	X[c]	X		X		X	X		X	X	X		X	X
Screening safety[d]	X													
Pregnancy Test[e]	X	X		X			X		X	X	X		X	X
HIV Antibody Testing	X													
Blood immunologic samples[f]	X	X				X			X[g]		X			
Cervical Digene swabs[i,j]	X	X							X	X	X			
ThinPrep™ [h,i]	X	X				X			X	X	X		X	X
Colposcopy, lesion photograph[k]	X[l]	X							X	X	X		X	X
Ectocervical biopsy[m]	X										X[n]			
Surgical excision[m]											X[n]			
OP rinse, vaginal swabs		X									X			X
Intra-anal swabs[o]		X									X			
Inject VGX-3100/Placebo		X		X			X							
Post treatment assessment		X	X	X	X	X	X	X[q]	X					
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Distribute PDC		X		X			X							
Review PDC			X		X	X		X[q]						
PROs[p]		X	X	X	X		X	X[q]		X	X	X		X

[a] Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

[b] Full physical examination (PE) mandatory at screening and study discharge (Week 88), otherwise targeted physical assessment as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

[c] Screening vital signs must include a measured height and weight. Weight will be collected on Day 0, Weeks 4 and 12;

[d] Screening safety includes 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 45 days prior to Day 0;

[e] For WOCBP, a negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

[f] At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood per time point and 8 mL serum per time point at Screening, Day 0 and Week 8 (4 ml serum per time point at Week 15 and 36). A total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0.

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

[i] Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

[j] Collected prior to the ThinPrep™ sample;

[k] A photograph of the lesion with at least one attempt should done as follows: Acetic acid should first be applied to the cervix then photographs of the cervix and the associated lesion should be photographed prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit.

[l] Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy;

[m] Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 4 and 5);

[n] Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from screening and/or Week 36 specimen(s) (paraffin blocks or unstained slides) may be used for immunohistochemistry (IHC) and HPV testing;

[o] To be collected only if subject consents for intra-anal sample collection

[p] One or both PRO questionnaires (i.e. SF-36 and EQ-5D-5L) will be completed by subjects enrolled in USA, Canada, Mexico, Germany and UK at multiple visits during the study. Additional quality of life questions will be asked at the Week 40 phone call. Refer to Section 6.8 for details

[q] Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 HPV INFECTION, CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a HR HPV type [2, 3]. Up to 13000 women in the US alone are diagnosed with cervical cancer each year, which leads to an estimated 4120 deaths [4]. HPV-16 is the most common high-risk genotype and combined with HPV-18 these two genotypes are estimated to cause about 70% of all cervical cancers [5, 6].

Incident infection by HPV is characterized by ongoing viral replication and shedding and is associated with early histologic changes (grade 1 cervical intraepithelial neoplasia) when the female cervix is infected with HPV. Most cases of genital HPV infection clear spontaneously, but persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions of the cervix, HSIL which is inclusive of grade 2 and 3 cervical intraepithelial neoplasia (CIN2/3) [7]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [8, 9]. The basis for these changes are attributed to the viral proteins E6 and E7. Infected cells produce E6 and E7 constitutively which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia.

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade CIN caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [10]. This means that the large number of women who already have high grade cervical dysplasia, either because they were too old to have received the prophylactic vaccine or they didn't respond to vaccination, must currently only rely upon surgery and the chance of spontaneous regression to treat their condition and avoid progression to cancer. Furthermore, the number of US-eligible teenagers who complete the prophylactic vaccination series remains low; 39.7% of US girls ages 13-17 completed their prophylactic HPV immunization series in 2014, which leaves a potentially vulnerable, under-protected population [11]. The current approaches to the management of cervical HSIL typically require surgery (i.e. LEEP/LEETZ, laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100 is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

1.1.2 VGX-3100

VGX-3100 contains plasmids that encode HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was water for injection with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This WFI/LGS formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100[3] was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This SSC formulation of VGX-3100 was administered to 116 subjects in a Phase 1 clinical trial, HPV-101. In study HPV-101, three 6 mg doses of VGX-3100 as the SSC formulation were delivered IM followed by EP with CELLECTRA™ 5P to healthy adults. Based upon interim analysis data at study Week 14, the SSC formulation is considered non-inferior to the WFI/LGS formulation based upon a 2-fold rise in overall Spot Forming Units (SPU) to the antigens encoded by the plasmids per 10^6 Peripheral Blood Mononuclear Cells (PBMC) as measured from baseline to Week 14 using the interferon-γ ELISpot assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (WFI/LGS formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or HPV-18. The Phase 2b study, HPV-003, enrolled and dosed 167 subjects with high grade cervical dysplasia from seven countries and one United States Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, United States and Puerto Rico). Subjects were randomized in a 3:1 ratio to the treatment arm (VGX-3100, WFI/LGS formulation) or the placebo arm, respectively. All subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to CIN1 or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol and modified intent to treat analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.3 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses

[3] Designated in earlier version of the HPV-301 protocol as VGX-3100X

creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [12, 13]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [14, 15]. This technology has been used for more than three decades by molecular biologists for cell transfection and has demonstrated versatility in use, as shown by its functionality in combination with a range of molecules, tissue types, disease indications, and across species [16].

The CELLECTRA™ device developed by Inovio is used for investigational purposes to administer plasmid-based DNA, in both prophylactic and therapeutic settings. Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency, and has demonstrated that the device helps to elicit favorable immunogenicity in several species (e.g., mice, pigs, and rhesus macaques) [17, 18].

VGX-3100, WFI/LGS formulation, has been administered throughout Phase 1 and Phase 2 investigations with the CELLECTRA™ 2000 device. A next generation device, CELLECTRA™ 5PSP, will be used in Phase 3. Both designs of the CELLECTRA™ device enhance the intracellular uptake of VGX-3100 by the delivery of electrical current, and the electrical current delivery and pulse pattern (electroporation) is identical in both designs. CELLECTRA™ 2000 involves a manual injection of VGX-3100 while the CELLECTRA™ 5PSP device will automate the intramuscular delivery of VGX-3100 and delivery of the EP pulses triggered by a single button press. Neither the dosage nor volume of VGX-3100 administered differs between the two devices. Administration of VGX-3100 with the CELLECTRA™ 5PSP also allows selection of the array needle length (13, 19 or 25 mm) depending on the estimate of the recipient's subcutaneous fat and muscle tissue.

The technology differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design are not significant and do not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, environmental specifications, and sterilization or performance specifications. The material changes are to the outer housing of the device and not to patient-contacting materials.

Benchtop design verification testing and a non-significant risk device functionality study was completed prior to Phase 3 to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™ 5PSP device design meeting its safety and performance specifications, and no change to the administration of VGX-3100 by electroporation. Inovio's device experience demonstrates that delivery of electroporation pulses into muscle immediately following injection of DNA plasmids is well-tolerated in humans and no significant safety issues have been identified [19-21]. The CELLECTRA™ 5PSP device is CE Marked in the European Union. For further information concerning the 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.4 SELECTION OF STUDY DESIGN

This Phase 3 study employs a prospective, randomized, double-blind, placebo controlled study design to further demonstrate the safety and efficacy of VGX-3100 followed by EP in women with cervical HSIL associated with HPV-16/18. The primary clinical hypothesis is that VGX-3100 is

a surgery-sparing, therapeutic option for the treatment of cervical HSIL and the underlying, pathogenic HPV-16/18 infection, which is supported by the findings of the Phase 2b trial. A placebo-controlled study is selected for this trial because it provides scientific rigor to distinguish an effective treatment, particularly in cervical HSIL for which spontaneous regression does occur.

1.2 DOSE AND REGIMEN RATIONALE

A total dose of 6 mg VGX-3100 DNA has been selected for this study based on previous human experience with both the WFI/LGS and SSC formulations of VGX-3100, preclinical data with VGX-3100 and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 2) without significant safety issues [19].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a true effect rather than random variation. Adverse events from previous human studies with VGX- 3100 (frozen formulation) and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in the Phase 2b study. The results obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Table 2. Percent of Protocol HPV-001 Subjects Responding and Average SFU/10^6 PBMC in Responders for each Antigen by Cohort in Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	%Response	AVG	%Response	AVG	%Response	AVG
HPV-16E6	33%	107	50%	243	50%	1341
HPV-16E7	17%	198	50%	104	67%	143
HPV-18E6	50%	359	50%	338	83%	664
HPV-18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

1.3 RISKS/BENEFIT ASSESSMENT

1.3.1 RISKS ASSOCIATED WITH CURRENT THERAPEUTIC OPTIONS

Currently, treatment of women with cervical HSIL usually consists of either surgical removal of the affected tissue by CKC, LEEP, ablative therapy via laser, or cryotherapy. All treatments for

cervical HSIL are associated with a variety of short and long term general and reproductive health risks as listed in Table 3.

Table 3. Risks Associated with Surgical Treatments for Cervical HSIL

Surgical Treatments for Cervical HSIL	**Risks**
CKC LEEP Ablative therapy (Laser or Cryotherapy)	Pain
	Exposure to anesthesia
	Heavy bleeding
	Infection
	Menstruation problems
	Cervical stenosis (can lead to alteration of squamo-columnar junction)
	Shortening of the cervix
	Decreased fertility/difficulty getting pregnant
	Cervical incompetence
	Pre-term birth and related low birth weight
	Incomplete treatment of cervical dysplasia
	Inadequate treatment of an occult early invasive cancer

Adapted from *FAQs Loop Electrosurgical Excision Procedure (LEEP) American College of Obstetricians and Gynecologists (2014) [11]*.

More importantly, none of the currently available surgical treatments for cervical HSIL eradicate the underlying cause of the high grade cervical dysplasia, persistent infection with one or more of the high-risk HPV types, and therefore, leaves patients at risk for recurrent cervical HSIL as well as high grade dysplasia of the vulva and vagina due to the potentially broader infection of the genitourinary area.

Although professional guidelines typically advocate immediate excisional therapy for adults with cervical HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [8]. The risk of a "missed diagnosis" of an occult early invasive cervical cancer exists for all current treatment modalities including surgical and ablative therapies. Furthermore, approximately 17-18% of patients with high grade CIN will experience recurrence of dysplasia following surgical intervention [8], which illustrates that current standard of care for cervical dysplasia requires improvement. The study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult early invasive cervical cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent cervical colposcopy, cytology and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced gynecologists, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

1.3.2 POTENTIAL RISKS OF STUDY PARTICIPATION

A risk associated with VGX-3100 for the treatment of high grade cervical dysplasia are the injection site reactions related to the IM injection and/or electroporation. Based on the phase 1

and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild (e.g. erythema) and limited to a few days in duration at most.

A second risk is the "delay" in "definitive treatment" of the high grade cervical dysplasia and the "missed diagnosis" of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not spontaneously regress. This risk is mitigated by careful serial cytology, HPV testing, and colposcopic exams, throughout the course of the study, and the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. Also, only investigators who are experienced in the management of cervical cancer will be chosen, and they will have the option of performing additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression.

A DSMB will also advise the Sponsor if it appears that the frequency of regression in the VGX-3100 group is unacceptably low compared to the placebo group. These measures should minimize the risk - even perhaps below that of standard care - of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. All subjects with suggestion of residual disease will undergo excisional therapy (e.g. CKC, LLETZ, LEEP) at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Tables 4 & 5) to provide histopathologic confirmation of regression. In the Phase 2b study, the rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

1.3.3 POTENTIAL BENEFITS OF STUDY PARTICIPATION

All currently accepted treatments for high grade cervical dysplasia are surgical procedures (LEEP, CKC, Laser ablation) which are all associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding and/or infection, damage to other organs, shortening and/or deformation of the cervix, pain, etc. Due to the risk of shortening and/or deformation of the cervix there are additional well accepted risks including cervical stenosis, infertility, cervical incompetence, preterm birth, and inability to visualize the transformation zone. Additionally, none of the surgical treatments systemically address the underlying oncogenic root cause, the high risk HPV infection in the lower genital tract, which leaves an underlying risk for further disease manifestations and transmission of HPV. VGX-3100+ EP is not associated with any of the risks associated with the surgical procedures outlined above (except for pain, which is transient and restricted to the deltoid/quadriceps treatment site) and has demonstrated the ability to not only eradicate the high grade dysplasia but also the ability to eradicate the underlying HPV infection. Subjects receiving placebo, who represent women of child-bearing potential, may benefit from the opportunity to be closely managed under careful surveillance over the course of this study and those who regress spontaneously will be able to avoid excisional therapy.

2 STUDY DESIGN

This Phase 3 study design is based upon the Phase 2b study design and results. HPV-301 is a prospective, randomized, double-blind, placebo controlled study to determine the efficacy, safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18.

A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming, based upon Phase 2b study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clears is 35% and 14% for VGX-3100 and placebo, respectively.

Subjects will be randomized in a stratified manner according to (a) the CIN severity observed in the biopsy specimens at screening (i.e. CIN2 vs. CIN3), (b) BMI category ($\leq$25 vs. >25 kg/m^2) on Day 0, and (c) age category (<25 years vs. $\geq$25 years) on Day 0. To ensure CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of cervical HSIL. Subjects must also have a cervical specimen test positive for HPV-16/18 by cobas™ HPV test to be eligible for participation in the study.

2.1 ENDPOINT ASSESSMENT

In the Phase 2b study, subjects were randomized 3:1 to the VGX-3100 frozen formulation arm or the Placebo arm. All subjects were scheduled to receive treatment on Day 0, Week 4 and Week 12 and undergo repeat cervical biopsy or surgical excision (i.e. LEEP, LLETZ, CKC) of the cervix at Week 36 to assess efficacy. The primary endpoint was histopathologic regression of cervical lesions to CIN1 or less at the Week 36 visit, and the secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less.

The primary endpoint for the Phase 3 study is based upon the results of the Phase 2b study. Given that HPV persistence is an important factor in the clinical progression of dysplasia and also based upon the findings of the secondary objective of the Phase 2b study, the responder definition for the Phase 3 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16/18.

The proportion of subjects who achieved this endpoint in the Phase 2b study was 35% (40%) of VGX-3100 subjects versus 14% (15%) for placebo, in an intention-to-treat analysis and modified intention-to-treat analysis, respectively. The composite endpoint of histologic regression and virologic clearance will be primary in the Phase 3 study, and histologic regression endpoint will be a secondary endpoint.

2.1.1 HISTOLOGY ASSESSMENT

Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Digital photographs of acetowhite lesions are also used to document colposcopic exam findings. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or by 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings as outlined in Tables 4 and 5 for subjects 25 years and above and below 25 years, respectively.

Table 4. Minimally Required Procedure at Week 36 for Subjects Age 25 Years and Above

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
25 and above	NA	NA	HSIL, ASC-H, AGC, Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	positive	Tissue Excision
	unsatisfactory	no lesion	LSIL, ASC-US	negative	4Q biopsy and ECC
	unsatisfactory	no lesion	NILM	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Table 5. Minimally Required Procedure at Week 36 for Subjects Under 25 Years

Age	Clinical and Laboratory Information at Week 28				Minimally Required Procedure at Week 36[a]
	Colposcopy		Cytology	HPV-16/18 Testing	
	Quality	Finding			
18-24	NA	NA	Carcinoma, AIS	NA	Tissue Excision
	unsatisfactory	lesion	NA	NA	Tissue Excision
	unsatisfactory	no lesion	HSIL, ASC-H, AGC	NA	Tissue Excision
	unsatisfactory	no lesion	NILM, ASC-US, LSIL	NA	4Q biopsy and ECC
	satisfactory	NA	LSIL, ASC-US, HSIL, ASC-H, AGC[b]	NA	4Q biopsy and ECC
	satisfactory	NA	NILM	positive	4Q biopsy and ECC
	satisfactory	NA	NILM	negative	4Q biopsy

Abbreviations: NA; not applicable because there is no impact to the decision at Week 36 due to a superseding finding; 4Q; four quadrant; NILM Negative for intraepithelial lesion and malignancy; ASC-US Atypical squamous cells of undetermined significance; AGC Atypical glandular cells; ASC-H Atypical squamous cells, cannot rule out high-grade lesion; AIS Adenocarcinoma-in-situ

[a] Any subject with prior ECC requires a negative ECC at Week 28 to allow 4Q biopsy and ECC, at minimum, at Week 36

[b] If cytology result is AGC "favor neoplasia", tissue excision is recommended

2.1.2 VIROLOGIC (HPV) ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28, 36, 62, and 88. Also, if there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for testing of HPV-16/18. Vaginal and oropharyngeal samples will be obtained to characterize HPV infection at Day 0 (prior to dosing) and at Weeks 36, and 88 to assess virologic response to treatment at sites other than the cervix. Intra-anal samples will be obtained (if subject consents to intra-anal sampling) to characterize HPV infection at Day 0 (prior to dosing) and at Week 36 to assess virologic response to treatment at sites other than the cervix.

2.1.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 6) for the primary endpoint takes into account both histopathologic regression of cervical HSIL and virologic (HPV-16 and/or HPV-18) clearance from cervical samples since HPV persistence is an important factor in the clinical progression of HSIL. The responder definition also excludes subjects who undergo excision or whose cervix is biopsied at any time between their initial dose and the Week 36 endpoint tissue collection. This exclusion is included to reduce the potential for artefactual increases in the treatment effect caused by removal of HSIL tissue and potentially HPV-16/18 by unplanned interval biopsies.

To qualify as a responder, the subject must have:

1. An acceptable histology specimen at Week 36, which is interpretable by the independent PAC, and
2. An acceptable HPV ThinPrep™ sample at Week 36, with an associated valid HPV-testing result.

A responder is defined as a subject with:

1) No histologic evidence of cervical HSIL
2) No evidence of HPV-16 and/or HPV-18 at the Week 36 evaluation
3) The subject must not have had an unscheduled excision or biopsy sample obtained between initial dose and the Week 36 evaluation.

Conversely, the following will designate the subject as a non-responder:

1) Histologic evidence of cervical HSIL at the Week 36 evaluation, OR
2) Evidence of HPV-16 or HPV-18 at the Week 36 evaluation, OR
3) An excision or biopsy sample obtained between initial dose and the Week 36 evaluation OR
4) Lack of either an acceptable Week 36 histology specimen or HPV ThinPrep™ sample.

Table 6. Definition of Primary Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 and/or HPV-18 at Week 36[b] AND Subject in which an excision or biopsy sample[c] was NOT obtained between initial dose up to Week 36 primary endpoint visit	Subject with histologic evidence of cervical HSIL, AIS, or cervical carcinoma at Week 36 evaluation OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 primary endpoint visit OR Subject with no Week 36 primary endpoint sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

[b] The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the time frame determines the HPV clearance endpoint.

[c] Excludes ECC-only samples

Responder and non-responder definitions for the secondary efficacy endpoints are detailed in Table 7 – Table 11.

Table 7: Definition of Secondary Regression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL[a] at Week 36 visit[b] **AND** Subject in which an excision or biopsy sample[c] was NOT obtained between initial dose up to Week 36 visit	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 visit **OR** Subject in which an excision or biopsy sample[c] was obtained between initial dose up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

[b] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.

[c] Excludes ECC-only samples

Table 8: Definition of Secondary Complete Regression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL squamous atypia, or LSIL at Week 36 visit[a] **AND** Subject in which an excision or biopsy sample[b] was NOT obtained between initial dose up to Week 36 visit	Subject with histologic evidence of cervical HSIL, squamous atypia, LSIL, AIS, cervical carcinoma at Week 36 visit **OR** Subject in which an excision or biopsy sample[b] was obtained between initial dose up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.
[b] Excludes ECC-only samples

Table 9: Definition of Secondary Non-progression Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of a worsening of cervical condition at Week 36 visit[a] relative to baseline **AND** Subject in which an excision or biopsy sample[b] was NOT obtained between initial dose up to Week 36 visit	Subject with histologic evidence of worsening of cervical condition at Week 36 visit relative to baseline **OR** Subject in which an excision or biopsy sample[b] was obtained between initial dose up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint.
[b] Excludes ECC-only samples

Table 10: Definition of Secondary Complete Regression and Clearance Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of cervical HSIL, squamous atypia, or LSIL[a] at Week 36 visit and no evidence of HPV-16 and/or HPV-18 at Week 36 visit[b] **AND** Subject in which an excision or biopsy sample[c] was NOT obtained between initial dose up to Week 36 visit	Subject with histologic evidence of cervical HSIL, squamous atypia, or LSIL AIS, cervical carcinoma at Week 36 visit **OR** Subject with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in which an excision or biopsy sample[c] was obtained between initial dose up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL
[b] The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the time frame determines the HPV clearance endpoint.
[c] Excludes ECC-only samples

Table 11: Definition of Secondary Clearance Endpoint Responder and Non-Responder

Responder	Non-Responder
Subject with no histologic evidence of HPV-16 and/or HPV-18 at Week 36 visit[a] **AND** Subject in which an excision or biopsy sample[b] was NOT obtained between initial dose up to Week 36 visit	Subject with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in which an excision or biopsy sample[b] was obtained between initial dose up to Week 36 visit **OR** Subjects with no Week 36 visit sample result

[a] The efficacy time frame is defined by those who have undergone HPV testing at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample within the time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the time frame determines the HPV clearance endpoint.
[b] Excludes ECC-only samples

2.1.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100 treatment will be evaluated in blood samples taken at baseline (both screening as well as Day 0 prior to dosing) and at Weeks 15 and 36. Cervical tissue samples will also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (screening).

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immunohistochemistry (IHC). Whenever possible, these studies may be performed on tissue sections from the diagnostic screening biopsy (pre-dose) and from tissue obtained post-dose(s) (Week 36).

2.2 TREATMENT PLAN

The three dose regimen of VGX-3100 appeared to be safe and well tolerated in the Phase 2b study, therefore all eligible subjects who consent to participate in the Phase 3 study will receive the same three 6 mg doses of VGX-3100 refrigerated formulation or placebo administered in 1 mL IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third (final) study treatment will be administered at Week 12 which is consistent with the Phase 2b study. The first study treatment will be given as soon as possible following confirmation of the cervical HSIL diagnosis and HPV-16/18 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-16/18.

2.3 SAFETY MONITORING PLAN

Although cervical HSIL is thought to require years to progress to cervical cancer, subjects in the Phase 2b study were followed closely throughout. HPV testing (Weeks 14 and 24), cytology (Week 14) and colposcopy (Week 24) were all mandatory during the observation period prior to obtaining tissue for determination of the primary histologic endpoint at Week 36. Investigators were also instructed to perform additional testing (including biopsy) if disease progression was suspected. These instances were infrequent as only 11 unscheduled biopsies were deemed necessary over the course of the Phase 2b study. In addition, the rate at which occult microinvasive cancer was discovered after 36 weeks was less frequent than what is reported in the literature [22]. Both observations would imply that the mandatory monitoring employed in the Phase 2b study was sufficient; however cervical disease will be monitored even more closely in this Phase 3 study. Colposcopy, cytology and HPV testing will be required at 8 to 14 week intervals throughout the observation period leading up to the primary endpoint 36 weeks after the first dose. Although less frequent monitoring may be adequate, the more frequent monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy.

Safety monitoring will include:

- Local and systemic events for 7 days following each treatment as noted on a Participant Diary Card (PDC).

- All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study;

In the Phase 2b study, the safety profile was carefully evaluated and treatment with VGX-3100 was well-tolerated based on observations through Week 88 in all subjects. The most common adverse events were administration-site reactions, which included pain, tenderness, erythema and swelling, and were generally mild and limited to a few days in duration. Only erythema showed a statistically higher incidence in VGX-3100 (78%) vs. placebo (57%) in the 7- and 28-day periods after a dose. One additional AE, sinusitis, was also statistically significantly increased over the course of the entire study period but resolved without sequelae in the VGX-3100 arm compared to the Placebo arm (10% vs. 0%).

As outlined above, safety monitoring and visit frequency has been designed to take into account the potential risk of delay in the usual treatment of the high grade cervical dysplasia and also the potential for a missed diagnosis of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not regress. Serial cytology, HPV testing, and colposcopic exams are applied throughout the course of the study with the well accepted understanding that cervical dysplasia progresses slowly, typically over years, which makes close, active follow-up possible. All subjects with suggestion of residual disease will undergo excisional therapy by LEEP or CKC at Week 36 as part of the efficacy assessment. Subjects whose cytology, HPV testing, ECC results (if applicable) and colposcopic exam suggest disease regression will undergo 4 quadrant biopsy or 4 quadrant biopsy with ECC (based upon Table 4 and 5) to provide histopathologic confirmation of regression. The use of a 4 quadrant biopsy in Phase 3 is a change from the approach used in Phase 2b to optimize the evaluation of histopathologic regression taking into consideration the inherent limitations of colposcopy and tissue biopsy samples in the absence of visible lesions [23].

In the Phase 2b study, the cervical tissue sample was initially read by a local pathologist and/or central pathology laboratory for rapid local medical management. The definitive histopathologic assessment was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US. Seven reports included the terms '(adeno)squamous cell carcinoma' or the premalignant condition of 'adenocarcinoma in situ' (AIS) in the final Phase 2b study results which included all 88 weeks of follow up. Three of the cases were reported as AIS, (2 VGX-3100, 1 placebo), out of which two cases (1 VGX-3100, 1 placebo) were confirmed as AIS by the Pathology Adjudication Panel. AIS is a pre-invasive glandular lesion which can be difficult to capture on standard of care screening with initial punch biopsy and is more commonly identified by full excision (e.g. LEEP, conization). There were four reports that included the term squamous cell carcinoma, of which two were confirmed by the Pathology Adjudication Panel, both in the VGX-3100 group. The other two cases (1 VGX-3100, 1 placebo) were diagnosed as CIN3 by the Pathology Adjudication Panel. The rate at which microinvasive cancer was found in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy was 1.8%, (2/114 with specimens), which is consistent with and even lower than the rate of 6.7% that has been reported under standard of care settings [22].

Importantly, investigators in the Phase 3 study will be chosen only if they are experienced in the management of cervical cancer as was the case in the Phase 2b study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analysis as outlined in Table 6. These measures should minimize the risk of progression of cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. The frequency of close monitoring by experienced investigators should minimize the risk of cancer progression on the study what is expected with standard of care.

2.3.1 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will be scheduled to meet quarterly. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that the proportion of the subjects with regression in the VGX-3100 group is unacceptably low compared to the placebo group; no formal interim analysis will be performed for this purpose.

2.4 LONG TERM FOLLOW UP PLAN

In the Phase 2b study, all subjects were scheduled to be followed for 1 year after the histopathologic assessment for the primary endpoint (to study Week 88). The establishment of efficacy based on histopathologic evidence dictated the removal of tissue at week 36 by either punch biopsy (ies) or more extensive surgical resection (i.e. LEEP, CKC). Subjects with colposcopic evidence of residual disease were to undergo LEEP/CKC. A higher proportion of patients who received placebo had a LEEP performed than those who received VGX-3100 (Table 12).

Cytology and HPV-16/18 clearance from the cervix was to be assessed at study Weeks 62 and 88 to evaluate for recurrence of dysplasia and HPV infection after removal of tissue at Week 36. Overall, in the phase 2b study, the majority of subjects had improved cytology and had cleared their underlying HPV-16/18 cervical infection by the Week 62 and 88 visits. For Weeks 62 and 88, there were no clinically meaningful differences noted between the subjects who received an excisional treatment (e.g. LEEP, CKC) and those that showed histopathologic regression and therefore only underwent a biopsy, as shown in Table 8 which summarizes the HPV and cytology results following Week 36.

Table 12. HPV-003 HPV and Cytology Results at Weeks 36, 62 and 88, mITT Population

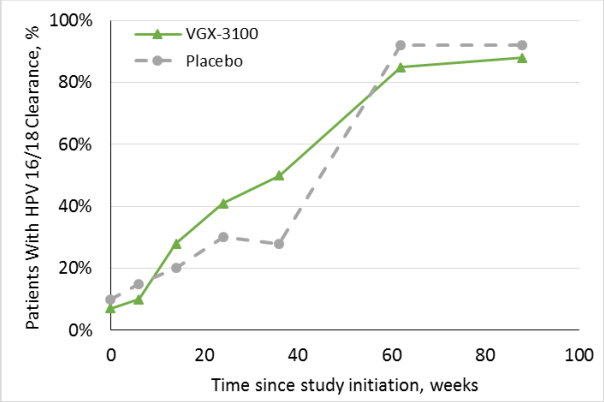
Week	Test[a]	VGX-3100		Placebo	
		LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	100% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89% (42/47)	89% (24/27)	100% (10/10)
88	Pap	96% (52/54)	91% (43/47)	85% (23/26)	100% (11/11)

Abbreviations: NA, not applicable, Pap smear was not done at Week 36
[a] HPV = HPV-16/18 testing; Pap = cytology testing
[b] LEEP or CKC done, at or before the study week as specified
[c] Only biopsy done, at or before the study week as specified

Clearance of HPV-16/18 from the cervix was observed in both treatment groups (Figure 1a) at similar rates until after the second dose when clearance in the VGX-3100 recipients continued to rise while the rate appeared to plateau in the placebo group.

Figure 1. HPV-16/18 Clearance and Pap Smear Findings in Phase 2b mITT Population by Treatment Group

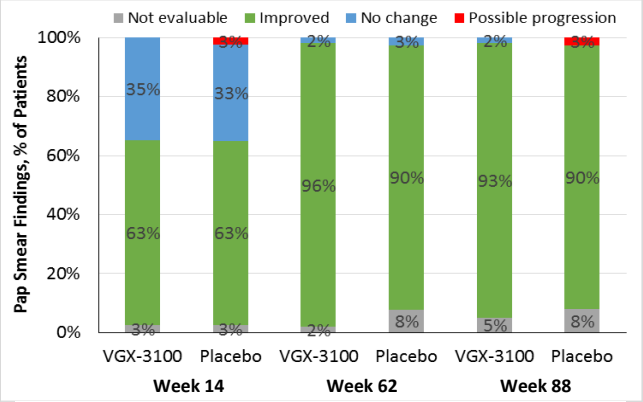
a.



No. of subjects

VGX-3100	123	62	118	116	115	108	103
Placebo	42	26	40	40	40	39	37

b.



No. of subjects

VGX-3100	118	108	103
Placebo	40	39	37

At Week 36, clearance was significantly higher among VGX-3100 subjects that had biopsy (63%) versus LEEP/CKC (41%), which likely reflects the association between clearance of the underlying HPV infection and the likelihood of having signs indicative of regression by colposcopic exam. HPV-16/18 clearance data (mITT population) post-Week 36 are described as follows: HPV-

16/18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% (42/51) for VGX-3100 post Biopsy only, 96% (27/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post Biopsy only. HPV-16/18 clearance at Week 88 was 89% (48/54) for VGX-3100 post-LEEP/CKC, 89% (42/47) for VGX-3100 post Biopsy only, 89% (24/27) for Placebo post-LEEP/CKC, and 100% (10/10) for Placebo post Biopsy only.

The majority of subjects had cleared their underlying cervical HPV-16/18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups. Forty-seven of 53 (89%) and 46 of 49 (94%) subjects at Weeks 62 and 88, respectively (mITT population) with histopathologic evidence of CIN2/3 regression (regressors) in the VGX-3100 treatment group experienced HPV-16/18 clearance. Despite the use of therapeutic resection for many VGX-3100 recipients whose CIN2/3 did not regress by Week 36 (non-regressors), HPV-16/18 clearance rates were notably lower (85% at Week 88) compared to regressors.

In the subjects who initially cleared HPV-16/18 by Week 36, only one HPV-16/18 recurrence was identified at the Week 62 and 88 evaluations. Specifically, one subject in the VGX-3100 group whose lesion was biopsied at Week 36 had HPV types 16 and 82 and CIN2 at screening, was HPV negative at Week 36, but tested HPV type 16 positive at Week 62, and then cleared HPV-16 at Week 88. The subject showed histopathologic regression at Week 36. No recurrences were identified in the eleven subjects in the placebo group whose lesions were biopsied at Week 36 with valid HPV data at Weeks 62 or 88. There were no (0/51) recurrences identified in the VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk as compared to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear cytology results at Week 62 were 93% (52/56) for VGX-3100 post-LEEP/CKC, 100% (51/51) for VGX-3100 post-Biopsy only, 93% (26/28) for Placebo post-LEEP/CKC, and 82% (9/11) for Placebo post-Biopsy only. At Week 62, cytopathologic improvement was reported for 104 of 125 (83%) subjects in the VGX-3100 treatment group and 34 of 42 (83%) subjects in the placebo treatment group (mITT population).

There were no instances of possible progression, and all cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. Improvement compared to study entry for Pap smear cytology results at Week 88 were 96% (52/54) for VGX-3100 post-LEEP/CKC, 91% (43/47) for VGX-3100 post-Biopsy only, 85% (23/26) for Placebo post-LEEP/CKC, and 100% (11/11) for Placebo post-Biopsy only. At Week 88, possible progression (atypical glandular cells) was reported in a single Placebo subject in the post-LEEP/CKC group (3%) and no subjects treated with VGX-3100. All other cases that did not meet the definition of improvement were due to either no change from baseline, sample considered not evaluable, or no data available. The majority of subjects showed improvement, and there was no meaningful difference between the Week 62 and Week 88 evaluations. These findings support that study subjects had no increased risk of progression based upon cytology as compared to standard of care.

The protocol-specified removal of dysplastic cervical tissue at Week 36 by either method substantially affected the clearance of HPV-16/18 and normalization of cytologic findings as expected, regardless of treatment group (Figure 1a, b). HPV-16/18 clearance rises at a sharp rate

after tissue is removed at Week 36 whether the excision is wide (e.g. LEEP, LLETZ, CKC) or more limited (biopsy). Notably, the method of tissue collection at the Week 36 endpoint did not appreciably affect the HPV-16/18 clearance rates beyond Week 36 (Table 8). Based upon the Phase 2b results, the risk of progression or recurrence of cervical dysplasia is low and comparable to the rates observed post-LEEP/CKC in clinical practice. The long term follow up planned for this Phase 3 study will include safety, cytology and HPV-16/18 testing at 6 months and also 1 year following the Week 36 histopathologic assessment, which is highly conservative given the expectation that few subjects will have persistent evidence of disease after the removal of tissue at Week 36 which is supported by the findings in the Phase 2b study.

2.5 GROUP-LEVEL UNBLINDING

Group-level unblinded (VGX-3100, Placebo) summaries and analyses of efficacy will be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. Long-term follow-up data will continue to be collected for all subjects with remaining visits through the final Week 88 visit. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and all other efficacy endpoints corresponding to the cervix and the Week 36 visit on which to make decisions regarding the VGX-3100 program, while still gathering secondary and exploratory endpoint and safety data through the final Week 88 visit. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance, b) the secondary endpoint of histopathologic regression, c) the secondary endpoint of virologic clearance, d) the secondary composite endpoint of histopathologic regression to normal and virologic clearance, e) the secondary endpoint of histopathologic regression to normal, and f) the secondary endpoint of histopathologic non-progression. None of these summaries or analyses will be provided if the total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group relative to this total count is less than 3% for a given summary/analysis. Also, items a) through f) are planned to be produced in the order in which they are listed, but as there are intersecting endpoints among these items, items among b) through f) will not be produced if the difference in total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group is 0, relative to any preceding item in the set. The group-level unblinded (VGX-3100, Placebo) production of the summaries and analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), PPD, which has already been providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded with respect to subject treatment assignment throughout the trial.

3 HYPOTHESIS AND STUDY OBJECTIVES

3.1 HYPOTHESIS

Three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered IM followed by EP with CELLECTRA™ 5PSP to adult women with histologically

confirmed HSIL of the cervix, associated with HPV-16 and/or HPV-18 will result in a higher percentage of women with histopathological regression of cervical HSIL lesions to no evidence of cervical HSIL and virologic clearance of HPV-16/18 compared to placebo delivered IM followed by EP with CELLECTRA™ 5PSP at the Week 36 visit.[4]

3.2 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
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	Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit

[4] The time frame is defined as any time starting from 14 days prior to the protocol-specified target date of Week 36.

3.3 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1.Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP	1a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)
	1b. Incidence and severity of all adverse events including SAEs (e.g. SUSAR, UADE and other unexpected AEs) for the duration of the study (through Week 88 visit)
2.Determine VGX-3100 efficacy compared to placebo as measured by **histopathologic regression of cervical HSIL**	2. Proportion of subjects with **no evidence of cervical HSIL** on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3.Determine VGX-3100 efficacy compared to placebo as measured by virologic clearance of HPV-16 and/or HPV-18	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit
4.Determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal	4. Proportion of subjects with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit
5.Determine VGX-3100 efficacy compared to placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18	5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6.Determine the efficacy of VGX-3100 compared with placebo as measured by histopathologic non-progression	6. Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7.Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations	7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (i oropharynx, vagina and intra-anal) at Week 36 Visit
8.Determine the humoral and cellular immune response to VGX-3100 compared with placebo at post dose 3, and Week 36 visits as assessed relative to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15, and 36 visits 8b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15, and 36 visits 8c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.4 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Endpoints
1. Evaluate tissue immune responses to VGX-3100 in cervical samples	1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Describe association of microRNA (miRNA) profiles, DNA methylation profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression	2. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits), miRNA profile (baseline, Week 8) and DNA methylation profile (baseline, Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100 compared with those treated with placebo	3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
4. Describe the patient-reported outcomes for subjects treated with VGX-3100	4. Patient-reported outcome questionnaires will be self-administered at baseline, Weeks 4, and 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK.
5. Determine whether a tissue-based score derived using an immunologic markers (Immunoscore) at baseline is predictive for histological and virological response to VGX-3100 at Week 36	6 Immunoscore results for VGX-3100 treated subjects and in conjunction with histological and virological outcomes at Week 36

4 SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Women aged 18 years and above and meets minimum age of consent per local regulations);
2. Confirmed cervical infection with HPV types 16 and/or 18 at screening by cobas^{TM} HPV test;
3. Cervical tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
4. Histologic evidence of cervical HSIL as confirmed by PAC at screening;
5. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;

6. Must be judged by Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision, 4-quadrant biopsy with ECC, or 4-quadrant biopsy) required at Week 36;
7. Satisfactory colposcopy at screening, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected CIN disease;
8. Cervical lesion that is accessible for sampling by biopsy instrument (e.g. Mini-Tischler device);
9. Cervical lesion of adequate size to ensure that a visible lesion remains after screening biopsy;
10. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening
    c) WOCBP is willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until Week 36. The following methods are acceptable:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism).
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle
        iii. Intrauterine device or intrauterine system
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject
11. Normal screening ECG or screening ECG with no clinically significant findings, as judged by the investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from enrollment in the study:

1. Microscopic or gross evidence of adenocarcinoma-in-situ (AIS), high grade vulvar, vaginal (inclusive of cervical HPV-related lesions that extend into the vaginal vault), or anal intraepithelial neoplasia or invasive cancer in any histopathologic specimen at screening;
2. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
3. ECC shows a potentially untreated carcinoma, untreated HSIL, indeterminate, or insufficient for diagnosis (ECC is not required to be performed as part of study screening);
4. Treatment for cervical HSIL within 4 weeks prior to screening;
5. Pregnant, breastfeeding or considering becoming pregnant through Week 36 visit;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, Silgard™, Cervarix™);
7. Presence of any unresolved abnormal clinical screening laboratory values of Grade 1 or greater per CTCAE v 4.03 and deemed clinically significant by the investigator within 45 days prior to Day 0;

8. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening (performed within 45 days prior to Day 0)
    b) Primary immunodeficiencies
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; (use of inhaled, otic, and ophthalmic corticosteroids are allowed)
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept)
    e) History of solid organ or bone marrow transplantation
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
    g) Subjects who are malnourished (i.e. medically significant unintentional weight loss, kwashiorkor, or marasmus) based on screening labs, medical history and physical exam per investigator's clinical judgment.
9. Receipt of any non-study, non-live vaccine within 2 weeks of dosing;
10. Receipt of any non-study, live vaccine (e.g. measles vaccine) within 4 weeks of dosing;
11. Current or history of clinically significant, medically unstable disease which, in the judgment of the investigator, would jeopardize the safety of the subject, interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);
12. Malignancy or systemic treatment for malignancy within 2 years of screening (with the exception of curatively treated, localized anogenital cancers and superficial skin cancers which are allowed);
13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
14. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
15. Sustained, manually confirmed, sitting systolic blood pressure >150 mm Hg or <90 mm Hg or a diastolic blood pressure >95 mm Hg at Screening or Day 0;
16. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at screening or Day 0;
17. Prior major surgery within 4 weeks of Day 0;
18. Participation in an interventional study with an investigational compound or device within 30 days of signing informed consent; participation in an observational study is permitted;
19. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
20. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
21. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);

22. Metal implants or implantable medical device within the electroporation area;
23. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
24. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
25. Active military service personnel;
26. Study-related staff or family member of study-related staff;
27. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests Grade 3 toxicity attributable to the study treatment, the medical monitor and Investigator will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All randomized subjects should be encouraged to complete all study treatments and follow-up visits. A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule for follow-up and treatment of HSIL (CIN2, CIN3), and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/ WITHDRAWAL

The investigator or study coordinator must notify the Sponsor within 24 hours if a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The investigator will make every effort to have

all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1 – Safety Parameters.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the CRF:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death of subject
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the CRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a medical need to withdraw the subject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject from participation in the study
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including telephone calls, letter sent by certified mail or equivalent.
- Other: The subject was terminated for a reason other than those listed above, such as the termination of the study by the Sponsor.

4.3.5 SUPPLEMENTATION OF STUDY SUBJECTS

If more than 10% of subjects from randomization of study treatment discontinue prior to the Week 36 primary endpoint procedures, then supplementation of study subjects will be considered.

5 STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The active and placebo formulations to be used in this study are described in Table 13. Both IPs will presented in clear glass cartridges and will be injected intramuscularly.

VGX-3100 and placebo will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 13. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Placebo	150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 BLINDING

This study is double-blinded with blinding maintained throughout the study by use of identical packaging for both the active product and the placebo. There is no difference in appearance for both the active product and the placebo.

The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is essential for proper clinical management of the subject, as judged by the investigator. It is preferred, but not required, that the investigator first contact the Medical Monitor to discuss options before unblinding the subject's treatment assignment. In case of non-emergency, investigator must contact Medical Monitor to discuss the options before unblinding the subject's treatment assignment.

The Sponsor's or designee's pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE, UADE, or AE of interest. No personnel directly involved with the study will be unblinded. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's treatment assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCT

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, double-panel label with tear-off. Both VGX-3100 and placebo labels will include, at minimum, the following information in Table 14:

Table 14. Example Labels for Investigational Product

Cartridges (primary container)	**Pouches** (secondary packaging)
VGX-3100 or Placebo Insert cap end IM administration Sponsor name	**LABEL BODY** Material ID/Study ID VGX-3100 or Placebo Single-use cartridge containing 1ml IM administration via CELLECTRA® 5PSP Store at 5°C, expiration date Caution Statement Sponsor name and address **LABEL TEAR OFF** Material ID/Study ID VGX-3100 or Placebo Patient ID: _____ Date (DD/MMM/YYYY): _____ Must be used by (time): _____

5.4 HANDLING OF INVESTIGATIONAL PRODUCT

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Unless otherwise specified, IP will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Immediately upon arrival, IPs should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition.

Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

5.5 DISPENSING OF INVESTIGATIONAL PRODUCT

It is the responsibility of the Investigator to ensure that the IP is only dispensed to study subjects. It must be dispensed only from official study sites by authorized personnel according to local regulations.

When a subject is eligible for randomization, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration. The pouch must not be discarded until 1) administration is completed and 2) all pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator.

The device user manual and instructions for use will inform clinical personnel about placement of the IP cartridge into the device, as well as the steps for injection and electroporation.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at site per institution policy or returned to Inovio Pharmaceuticals, Inc. or its designee, if site cannot destroy IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor.

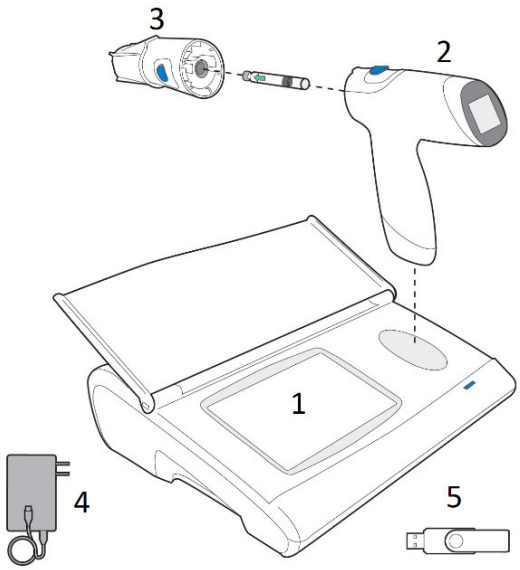
The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

If IP is returned to Inovio Pharmaceuticals, Inc., or its designee, it must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8 CELLECTRA™ 5PSP DEVICE

The Investigational product\placebo will be delivered using the CELLECTRA™ 5PSP device. The device consists of five (5) main components (see Figure 2):

Figure 2: CELLECTRA 5PSP Base Station with Handset



1) The 5PSP Base Station serves as a charging dock for the Handset and can accept limited data inputs as well as store records.

2) The reusable 5PSP Handset is battery powered and delivers the electroporation pulses. The Handset accepts the disposable array.

3) The 5PSP Sterile Single Use Array consists of five (5) needle-electrodes bonded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

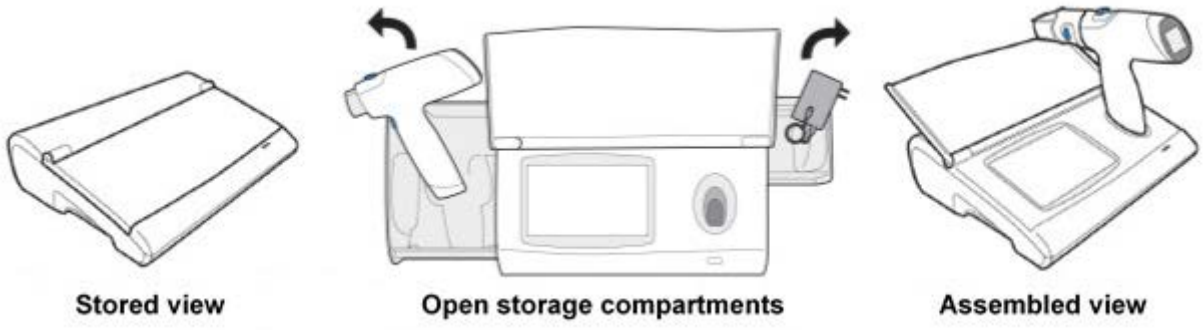
4) USB International Power Supply

5) Flash Drive used to transfer device logging data to the manufacturer.

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset. The base station is illustrated in Figure 3.

Figure 3: CELLECTRA™ 5PSP Base Station



<u>Handset</u>

The handset facilitates delivery of the needles for injection and the electroporation pulses into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the

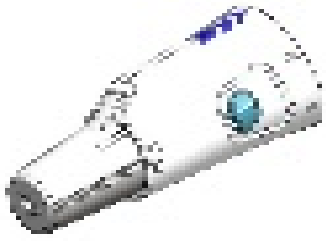
handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire. The handset is illustrated in Figure 4.

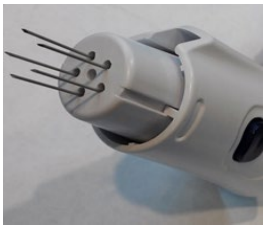
Figure 4: CELLECTRA™ 5PSP Handset

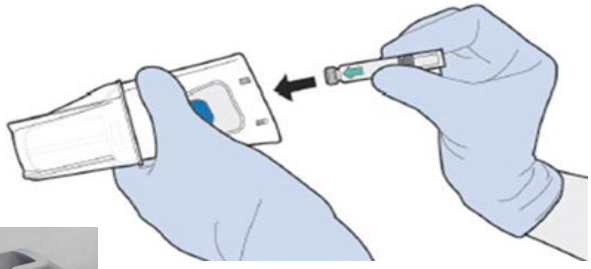
Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 intramuscular injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array (indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The array is illustrated in Figure 5. The array features no software.

Figure 5: CELLECTRA™ 5PSP Array







5.9 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of the device are located in the CELLECTRA™ 5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training. Training will include review of the device user manual as well as hands-on training. After training on the proper use of the CELLECTRA™ 5PSP device, intended users at each site will be required to demonstrate their competence in its use to Inovio or its designee. An instructional video has been prepared for review by site personnel on an as needed basis.

The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel.

Any deviation from the above procedures must be approved by the sponsor or its designee.

5.10 PACKAGING AND LABELING OF CELLECTRA™ 5PSP DEVICE

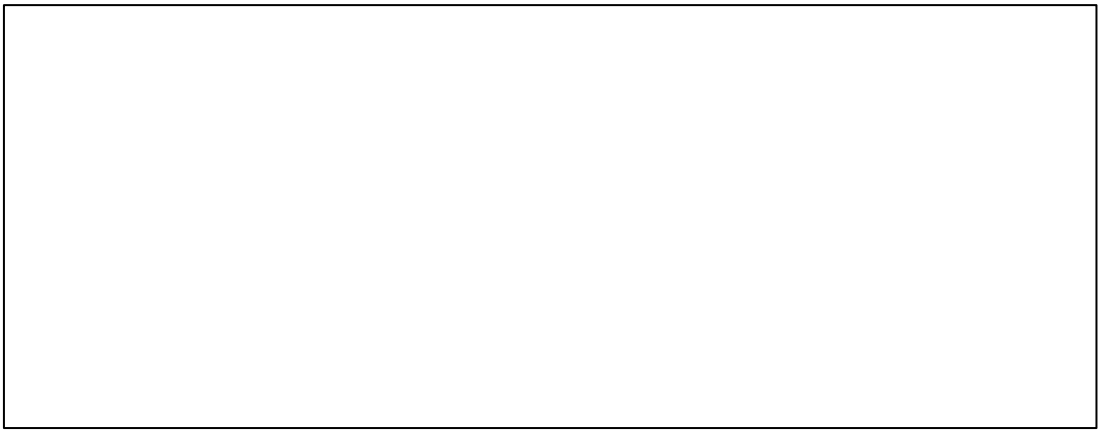
See below Figure 6 for example CELLECTRA™ 5PSP device component labels.

Figure 6. Device Labels (Base, Handset, Array)

BASE STATION

HANDSET

ARRAY



5.11 HANDLING OF CELLECTRA™ 5PSP DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual.

5.12 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of the device. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP serial number and array lot number. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.13 RETURN OF CELLECTRA™ 5PSP DEVICES

Upon completion or termination of Inovio studies, the Base Station and Handset must be returned to Inovio Pharmaceuticals, Inc.

Device components returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all device components identified above should be arranged by Inovio Pharmaceuticals, Inc. or the responsible Study Monitor.

Unused 5PSP Arrays may be either returned to Inovio or destroyed on site. If destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions will not be granted with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct.

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who have been identified with standard of care biopsy results of CIN 1/2, CIN 2, CIN 2/3 or CIN 3 and who consent to participate in the study will be eligible for screening and will have biopsy slides or tissue sent to the central pathology lab for review by PAC for evaluation prior to enrollment.

Additionally, Investigators may discuss with the Sponsor on a case-by-case basis the screening of subjects with abnormal cytology findings (i.e. HSIL or ASC-H with or without local HPV-16 or 18 genotype results) obtained as part of standard of care. The specific circumstances MUST be submitted in writing (e.g. email or fax) and the medical monitor MUST be consulted prior to screening a volunteer with these cytology findings (i.e. ASC-H or HSIL with or without HPV-16 or 18) for this study. The initial biopsy results may have been obtained at a referring institution by someone other than the site investigator.

- In the case where the subject has an ASC-H or HSIL cytology result without HPV-16 or 18 genotyping results available locally and if approved by Inovio, the site may proceed with initial study screening by sending ThinPrep™ samples to the central laboratory to screen for HPV 16/18 by cobas™ assay. A non-specific result from local testing of "Positive for high risk HPV" is not sufficient and will require the collection of the ThinPrep™ sample for HPV-16 and/or HPV-18 testing by cobas™ assay. If the central lab ThinPrep™ sample result is positive for HPV-16 and/or HPV-18, the site may continue screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.
- In the case where the subject has an ASC-H or HSIL cytology result with HPV-16 or 18 positive genotype results available locally and if approved by Inovio, the site may proceed with initial study screening including performing the initial colposcopy and biopsy. Biopsy tissue must be sent to the central pathology laboratory directly and not tested locally.

Subjects who consent to participate will have biopsy slides or paraffin-embedded tissue block(s) from a previous biopsy and/or newly collected cervical biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by PAC. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e.

slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

- Biopsy specimens and colposcopic photographs obtained within 10 weeks prior to Day 0 as part of standard of care before the informed consent may be used as part of the screening and evaluation process. If the pathology results of the initial biopsy obtained as part of standard of care are available confirming the presence of cervical HSIL (CIN2 or CIN3), those biopsy slides or sample(s) may be sent directly to the central pathology lab after the subject has signed the informed consent.

For those individuals diagnosed with cervical HSIL by a local pathologist, where the initial biopsy slides or tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable time frame, colposcopy should be performed and an additional biopsy sample collected during screening. A photograph of the lesion with at least one attempt should done as follows: Acetic acid should first be applied to the cervix then photographs of the cervix and the associated lesion should be photographed prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit.
The 10 week screening window begins upon collection of the biopsy sample that will be evaluated by the PAC.

Subjects must have a histologic diagnosis of cervical HSIL (CIN2 or CIN3) confirmed by the PAC and a screening ThinPrep™ cervical specimen test positive for HPV-16 and/or HPV-18 by cobas™ HPV test to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18. Subjects' post-menopausal status must meet requirements as specified in the inclusion criteria [24, 25]. The assessments during the screening period will determine the subjects' continued eligibility for the study and also their ability to comply with protocol requirements by completing all assessments.

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the safety laboratory collections/assessments, which must be performed within 45 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent
- Demographics; including age, and race/ethnicity
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- Full Physical Examination (including height, weight and BMI measurements)
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)

- Urine pregnancy test
- Colposcopy with lesion photography and/or cervical biopsy (Screening colposcopy and photography is optional if adequate colposcopy was performed upon collection of initial biopsy)
- 12-lead ECG (within 45 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 45 days prior to Day 0);
- Serology (HIV Antibody, within 45 days of Day 0)
- Determination of eligibility per inclusion / exclusion criteria
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluations will be performed on **Day 0 prior to study treatment:**

- Determination of eligibility per inclusion / exclusion criteria
- Randomization
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood (at least 34 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile (a total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0)
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) sample by oral rinse and vaginal swabs for HPV testing
- Intra-anal swabs (if subject has consented for intra-anal sampling) for HPV testing
- Colposcopy (accompanying lesion photography should be attempted at least once)
- Patient-Reported Outcome (PRO) questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

Study treatment will be administered and the following evaluations will be performed on **Day 0 post-treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)
- Download EP data from device within 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review Day 0 PDC (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.3 WEEK 4

The following study evaluation will be performed on **Week 4 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect PDC for dose 1

The following study evaluations will be performed **on Week 4 post treatment:**

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.5 WEEK 8

The following study evaluation will be performed during the visit

- Vital signs
- Targeted Physical assessment
- Collect and review PDC for dose 2
- Post treatment adverse event and injection site reaction evaluation

- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Whole blood (at least 34 ml) and serum (at least 8 ml serum) for immunology including miRNA profile

6.2.6 WEEK 12

The following study evaluation will be performed on **Week 12 prior to study treatment (±4 days):**

- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test

The following study evaluations will be performed **Week 12 post treatment**:

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Download EP data from device within 48 hours of study treatment
- PRO questionnaire (EQ-5D-5L only) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.7 8-14 DAYS POST DOSE 3 PHONE CALL

The following information will be evaluated during phone call:

- Post treatment adverse event and injection site reaction evaluation
- Review PDC for dose 3 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.2.8 WEEK 15

The following study evaluations will be performed on **Week 15 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Post-treatment injection site reaction assessment
- Urine pregnancy test
- Whole blood (at least 51 mL) and serum (at least 4 mL) for immunology
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be instructed to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Collect PDC

- Colposcopy (lesion photography should be attempted at least once)

6.2.9 WEEK 28

The following study evaluations/actions will be performed on **Week 28 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy (lesion photography should be attempted at least once) to assess for possible disease progression.
- ECC (only to be collected if ECC was done as part of Screening)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 28 visit by a subject enrolled in US, Canada, Mexico, Germany and UK only

6.2.10 WEEK 36

The following study evaluations will be performed on **Week 36 ± 1 week:**

- Targeted physical assessment
- Vital signs
- Socio-Behavioral assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Whole blood (at least 34 ml) and serum (at least 4 ml) for immunology
- Urine pregnancy test
- 2 Digene cervical swab samples
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) by oral rinse and vaginal swab for HPV testing
- Intra-anal swab (if subject has consented to intra-anal sampling) for HPV testing
- Colposcopy (lesion photography should be attempted at least once)
- Biopsy or surgical excision based on information collected at Week 28 to determine the minimally required tissue collection procedure (e.g. 4 quadrant biopsies, 4 quadrant biopsies and ECC, or surgical excision) to be used for histopathologic assessment at Week 36 as described in Tables 4 & 5
- PRO questionnaire (EQ-5D-5L only) completion by a subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.11 WEEK 40 PHONE CALL

The following study evaluations will be performed on **Week 40 ± 2 weeks** via a phone call:

- AE/SAE assessment

- Review of histology results as read by PAC from Week 36
- Completion of quality of life questions will asked to subjects enrolled in US, Canada, Mexico, Germany and UK only
- PRO questionnaires (SF-36 and EQ-5D-5L) completion 8-14 days post Week 40 by a subject by subjects enrolled in US, Canada, Mexico, Germany and UK only

6.2.12 WEEK 62

The following study evaluations will be performed on **Week 62 ± 2 weeks:**

- Targeted physical assessment
- Vital Signs
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Colposcopy (lesion photography should be attempted at least once)

6.2.13 WEEK 88

The following study evaluations will be performed on **Week 88 ± 2 weeks:**

- Full Physical Exam
- Vital Signs
- Socio-Behavioral Assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Urine pregnancy test
- ThinPrep™ sample for HPV typing and pap smear (subject should be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to sample collection)
- Oropharynx (OP) by oral rinse and vaginal swabs for HPV testing
- Colposcopy (lesion photography should be attempted at least once)
- PRO questionnaires (SF-36 and EQ-5D-5L) completion by a subject (if enrolled in US, Canada, Mexico, Germany and UK only)

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy

of the signed informed consent documentation must be provided to the subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with [redacted] (e.g., [redacted]). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.3 SAFETY EVALUATIONS

6.3.3.1 Physical Exam

A full physical examination (PE) will be conducted during screening and study discharge. It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

A targeted physical assessment will be performed at other visits as determined by the investigator or directed per subject complaints.

6.3.3.2 Vital Signs

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 Weight and Height

Weight and height will be collected at screening in order to calculate the BMI. Weight will be collected on Day 0, Weeks 4 and 12.

6.3.3.4 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. The medical history will include a) any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s), and b) if treated previously for CIN, the respective treatment type(s) and date(s).

6.3.3.5 Socio-Behavioral Assessment

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 36 and 88, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 Laboratory Evaluations

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- Serum glutamic-pyruvic transaminase (SGPT)/Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose $\geq$ 1+) a microscopic examination should be performed.

6.3.3.7 Demographics

Demographic information will be collected via self-report (unless noted otherwise), including the following:

- Age
- Race/ethnicity

6.3.3.8 Urine Pregnancy Testing

For subjects of reproductive potential, a negative spot urine pregnancy test is required prior to each study treatment, colposcopy and surgical excision.

6.3.3.9 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QTcb or QTcf, ST segment, T wave as well as an investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as "clinically significant (CS)" or "not clinically significant (NCS)" by the investigator.

6.3.3.10 Subject Self Evaluation

Subjects will be provided a PDC and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PDC will be reviewed with the subject by the study staff at 8 -14 days post-dose phone call and next in-person visit.

The study staff will review the PDC for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications.

Any PDC entry determined to meet the CTCAE criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. If the PDC entry does not meet the criteria of a Grade 1 or higher AE as per the CTCAE guidelines, clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the PDC entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a 3-dose series of either 1 ml VGX-3100 or Placebo by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with the CELLECTRA™ 5PSP. Study treatment must not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.4.1 RISKS OF TREATMENT PROCEDURES

A summary of the potential risks of IM administration followed by EP with the CELLECTRA™ 5PSP can be found in the VGX-3100 Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO TREATMENT

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at Day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

Medication taken for anxiety or pain management should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening will be performed for inclusion into the study as listed in section 6.1.1.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and at least 30 minutes after each study treatment and at 2 to 4 weeks post study treatment visits. They will also be advised to record local and systemic AEs for 7 days on a PDC.

An adverse event assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 15. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity***	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

*** Sponsor defines daily as impact lasting ≥ 24 hours

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, two previously-validated patient-reported outcomes (PRO) instruments will be provided to the subjects enrolled in US, Canada, Mexico, UK and Germany. The following two PRO questionnaires will be used:

1. Short Form Health Survey, **version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [26]
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [27, 28]

Either one or both PRO instruments (refer to Section 6.2) will be provided to the subject who will be instructed to complete the questionnaire at the following time points:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- Week 4 (after study treatment)
- 8-14 days post dose 2
- Week 12 (after study treatment)

- 8-14 days post dose 3
- 8 -14 days post Week 28
- Week 36 (after biopsy or surgical excision)
- 8-14 days post Week 40
- Week 88

Administration of PRO instruments will be performed according to the validated procedure and guidelines of each respective instrument, except for some assessments for exploratory analyses. Additional instructions will be provided separately.

Additional questions related to the subject's quality of life following surgery or biopsy will be completed at the Week 40 phone call for subjects enrolled in USA, Canada, Mexico, UK and Germany.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 8, 15, and 36.

Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine 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). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 as well as Week 8. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 8 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

Profiling of DNA methylation status will occur via the use of nucleic acid isolated from Digene brushes used at Screening, Day 0 and Week 15. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in DNA

methylation profiles that occur once dosing with VGX-3100 has finished to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immune assessment. Available tissue collected from pre- and post- treatment may be assessed for the presence of immune cells using immunohistochemistry or immunofluorescence. The presence of immune signatures may also be analyzed through the assessment of various transcripts suggestive of an inflammatory or an immunosuppressive tissue microenvironment.

An Immunoscore algorithm will be applied to cervical tissue obtained at baseline. The algorithm is composed of scoring patients based on infiltration of immune cells stained with CD8, FoxP3, CD103 and Perforin. Scoring will occur in epithelium designated as HSIL.

For HSIL epithelium, 1 point will be assigned for patients who show at least two of the following three parameters:

- CD8 count per mm^2 >375,
- perforin count per per mm^2 >0 and
- CD103 count per per mm^2 >150

Additionally, 1 point will be assigned for each for the following parameters:

- FoxP3/CD8 ratio <1:3,
- CD103/CD8 ratio >2:1,
- CD103/ perforin ratio >10:1 and
- CD103/FoxP3 ration > 1.5:1

6.11 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at the screening, Day 0, Weeks 8, 15, 28, 36, 62, 88 and read in a central laboratory. HPV typing including PCR by cobas™ HPV test will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer at Day 0, Weeks 15, 28 or 36, the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from any sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples to eliminate potential interference with the results of HPV testing.

At visits (i.e. Screening, Day 0, and Weeks 15, 28, and 36) where multiple cervical samples are collected, the two Digene cervical swab will be collected prior to the ThinPrep™ sample. Immunology testing may be performed from Digene swab.

Details of sample collection and shipment information will be provided in the laboratory manual.

Additionally, if there is residual tissue available from cervical tissue from screening and Week 36 after the histologic diagnosis have been rendered, then unstained slides and/or paraffin blocks may be collected to test for HPV typing.

Also, non-cervical swabs (i.e. oropharyngeal rinse, vaginal brush and intra-anal swabs) will be collected at specified visits for HPV typing.

6.12 COLPOSCOPY AND CERVICAL BIOPSIES

Colposcopy at screening must be adequate, defined as full visualization of the squamo-columnar junction (Type I or II transformation zone) and complete visualization of the upper limit of aceto-white epithelium or suspected dysplasia. An ECC is not required for study entry. However, if an ECC was done as part of routine care during the screening period, and found to have evidence of cervical HSIL such subject should not be enrolled in the study. Colposcopy is not required to be performed at screening if adequate colposcopy was previously obtained upon collection of initial biopsy. All colposcopies performed after informed consent should be conducted according to the guidelines outlined in Appendix A.

Interval colposcopies will be performed at Day 0, Weeks 15, 28, 36, 62, and 88. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

At least one attempt to photograph the lesion should done as follows: Acetic acid should first be applied to the cervix then photograph(s) of the cervix and the associated lesion should be taken prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit. Pictures should be taken to obtain a quality image to the extent feasible according to investigator judgment.

If a biopsy or surgical excision is performed, images of the cervix should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach and 2) the process for uploading the images to a secure server. Additionally, if a vaginal or vulvar lesion should develop after a subject is enrolled, photographs should also be taken to document the clinical exam finding.

6.12.1 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at screening to confirm eligibility. If the criteria outlined in Table 4 or 5 are met, ectocervical biopsies may also be performed at Week 36 to provide tissue for histopathologic assessment of disease regression.

Visualization of a normal appearing cervix by colposcopy is insufficient evidence to confirm disease regression at Week 36. Biopsy must be performed at the location of the screening biopsy if no disease is visible at Week 36.

Biopsies should not be performed at any other visit unless there is suspicion of disease progression. Removal of additional tissue by biopsy before Week 36 will bias results toward improvement regardless of whether the subject is in the active or placebo group. The bias introduced will obviously be more significant for smaller lesions. For this reason, if biopsies are obtained prior to Week 36, the subject will be classified as a non-regressor in the efficacy

analyses. Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy prior to Week 36, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.12.2 UNSCHEDULED BIOPSIES

In the event an unscheduled biopsy is performed after the initial dose and prior to Week 36, the subject will be classified as a non-responder. The subject will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and the Investigator's judgment based on the results of the histological diagnosis from the unscheduled biopsy. Additional instructions for collecting ectocervical biopsies are detailed in Appendix A. All biopsy samples/excised tissue will be sent to the central pathology lab for review by PAC.

6.13 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to the screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.14 RESTRICTIONS

6.14.1 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled otic and ophthalmic corticosteroids are allowed
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine
- Blood thinners (e.g. anticoagulants, antiplatelet drugs) or other medication that affects blood clotting within 2 to 14 days (e.g., 4-5 drug half-lives) of any study treatment, biopsy or excisional procedure (e.g. LEEP)

6.14.2 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep™ samples.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal death, still birth, congenital anomaly of the fetus/newborn); see Section 7.1.9 for additional information on pregnancy reporting.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.

- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.2.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does

not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.

7.1.2.2 Event Reporting for Disease Progression or Exclusionary Histologic Findings Post-study Treatment

After starting study treatment, if there is histologic confirmation of progression of cervical HSIL to micro invasive or invasive squamous cell carcinoma, the event must be reported as an SAE. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances, the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.3 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.4 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

For countries recognizing and regulating CE Mark devices, SAEs related only to the device which meet the medical device vigilance (MDV) reporting criteria will be handled by the Sponsor under the post-market surveillance/vigilance reporting requirements per MEDDEV 2.12-1. In such cases, the Sponsor will report as per the regulations to the relevant health authorities that require MDV reporting.

7.1.5 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported.

The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life Threatening)
- Grade 5 (e.g. Death)

The investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Please refer to Table 15 Grading Scale for Injection Site Reactions in Section titled "Assessment of Injection Site Reactions" above.

7.1.6 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the CELLECTRA™ 5PSP device. An AE may also be assessed as not related to the IP and/or the device. Because the investigator is knowledgeable about the subject

(e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the device indicating "yes" or "no" accordingly. Causality should be assessed by the investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event.

7.1.7 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

7.1.8 POST-STUDY REPORTING REQUIREMENTS

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.9 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to Week 36 will be excluded from participation in the study. Should a subject become pregnant after receiving the first study treatment in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor or its designee within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax, as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF THE COLLECTION AND RECORDING OF SAFETY DATA

Non-serious AEs and SAEs (and UADEs) will be collected for each subject from the time when informed consent is obtained through Week 88.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE (or UADE) occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100/placebo delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

- Grade 3 or greater persistent administration site erythema, and/or induration recorded ≥ 2 hours immediately after Study Treatment
- Grade 4 or greater persistent administration site pain, tenderness recorded ≥ 2 hours immediately after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

Sites will inform the Sponsor via method described in section 7.4.1 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

- If at any time during a study one-third (1/3) or more of the subjects experience an AESI, verified per protocol definition, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB. Only the DSMB may review unblinded data in making their recommendation to the Sponsor regarding continuation of a trial.

- If any SAE (or potentially life-threatening AE), or death verified as related to study treatment occurs, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

- If three or more subjects in this study, experience the same Grade 3 or 4 unexpected adverse event, verified per protocol definition and assessed as related to study treatment, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, verified per protocol definition and assessed as related to study treatment, further enrollment and study treatment will be

halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

The sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing clinical abnormalities are in Section 7.1 in general and in the Table provided in Section 7.1.5.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

7.4 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the AE CRF.

7.4.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) (see Section 7.3.1) require expedited communication from the Site to the Sponsor. Within 24 hours of the site's awareness of the event, AESI must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the investigator must notify the Sponsor via email or phone.

AESI reporting if EDC system is unavailable

EMAIL:	[redacted]
SAFETY PHONE:	[redacted]

7.4.2 STUDY REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure.

An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.3 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.4 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to the Sponsor or the appropriate designee.

Within 24 hours of the site's awareness of the event, all SAEs (regardless of relationship to investigational product) must be reported by the Investigator through data entry in the Adverse Event electronic case report form (eCRF) via the Medidata RAVE electronic data capture (EDC) system. In the event that the Medidata RAVE EDC system is unavailable, the paper SAE Report form should be used and faxed to the PPD Pharmacovigilance (PVG) Safety Hotline Fax Number shown below:

Facsimile (FAX) reporting if required[a]:

Americas FAX#: [redacted]
Europe FAX#: [redacted]

a: Reporting by FAX is required for paper SAE Report Forms if electronic data capture (EDC) is not available, redacted supporting medical records, and Pregnancy Report Forms.

All supporting documents for SAE reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor. The supporting documents for SAE reports should be sent by fax to the PPD PVG Safety Hotline Fax Number, shown above.

Investigator will supply the Sponsor and the IRB with more information as it becomes available and any additional requested information. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.3 and 7.1.4).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor with 10 days of discovery. Any product complaint that involves an AE or SAE must be also reported per Section 7.4.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation.

Additional instructions on reporting to be provided separately.

7.5 STUDY DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8 STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects with a histologic diagnosis of cervical HSIL. The study's primary endpoint is binary: regression to CIN1/normal and clearance of HPV-16 and/or HPV-18 infection, based on tissue collected at Week 36. The primary hypothesis is that VGX-3100 will be superior to placebo regarding the proportion who achieve the primary endpoint. Secondary efficacy analyses involve regression to CIN1/normal, clearance of HPV-16 and/or HPV-18 infection from cervical tissue and non-progression of cervical lesions. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, association of colposcopy, cytology, virology, other microRNA (miRNA) profiles, and DNA methylation profile and efficacy, patient-reported outcomes, and association of Immunoscore and efficacy.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized (2 VGX-3100:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) BMI category

(≤25 vs. >25 kg/m^2) on Day 0, and c) age category (<25 years vs. ≥25 years) on Day 0. There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled. A group of sequential allocation numbers will be designated for use by each participating country.

The study is double-blinded.

8.3 SAMPLE SIZE/POWER

A sample of 198 subjects will be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 35% and 14% for VGX-3100 and placebo, respectively. These proportions also incorporate missing data (~10%) classified as non-regressors (failures). The assumptions are based on the Phase 2 study results.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The intention to treat (ITT) population includes all subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be primary for the analysis of efficacy in this study.
- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding ITT population for the analysis of efficacy.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding ITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for

categorical variables, by treatment arm, for the ITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date; start dates will not be imputed. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true population probabilities of the primary endpoint for VGX-3100 and Placebo, respectively. The primary hypothesis of superiority is:

$$H_0: \delta \leq 0 \textit{ vs. } H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [29]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

The secondary efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. It also includes subjects who undergo early excision or biopsy on or after Dose 1 but prior to this time frame or subjects who have no endpoint data for this time frame; these subjects are considered as failures for the efficacy endpoints. Table 7 through Table 11 provide details for the definition of the endpoint responses.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and also the secondary efficacy endpoints of regression and clearance individually and the Immunoscore results. Relationships will be examined by using logistic regression models which model the efficacy outcomes versus the Immunoscore results and treatment group as regressor variables.

An exploratory analyses will examine the relationship between the primary efficacy endpoint and a) miRNA results, b) DNA methylation results, c) colposcopy results, d) cytology results, and e) HPV results. Relationships will be examined by using logistic regression models which model the primary endpoint outcome versus these results and treatment group as regressor variables.

Other exploratory analyses will examine durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue at Weeks 62 and 88. Descriptive statistics will be utilized; percentages of subjects who cleared will be presented by time point or anatomic location and treatment group.

8.10 IMMUNOGENICITY ANALYSES

Post-baseline cellular and humoral responses will be compared between treatment groups using a difference in medians and associated exact non-parametric 95% CI. Increases from baseline in interferon-γ ELISpot response magnitudes and HPV E6 and E7 titers from ELISA at Weeks 15 and 36 visits will be evaluated. Increases from baseline in CD8+ / CD137+ PBMCs Perforin+ results at the Week 15 visit will be evaluated.

Changes from baseline in tissue response will be compared between treatment groups using a difference in means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

The mITT population will be used for immunogenicity analyses.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 28 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [29]. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

For AE data, partial start dates will be imputed to the date of treatment to conservatively report the event as treatment-emergent, whenever the portion of the date is consistent with that of the study treatment. Otherwise, it will be imputed to the earliest date consistent with the partial date. A completely missing onset date will be imputed as the day of treatment. Partial stop dates will be assumed to be the latest possible day consistent with the partial date.

AE duration will be calculated as (Stop Date – Start Date) + 1.

8.12 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration.

8.13 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the ITT population.

8.14 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes will be compared between treatment arms, based on PRO endpoints. Median changes from baseline for the SF-36 and EQ-5D-5L responses and median days of worsened quality of life for the Week 40 Quality of Life questionnaire will be analyzed using exact non-parametric 95% confidence intervals for the differences in medians. The proportion of subjects who report a worsened quality of life for the Week 40 Quality of Life questionnaire will be analyzed using a 95% Miettinen and Nurminen confidence interval for the difference in proportions.

In addition, the Week 36 and beyond outcomes will be summarized according to those with excision versus those without excision.

The mITT population will be used for PRO analyses.

8.15 MISSING VALUES

Missing data will be considered as non-regressors (failures) for the ITT efficacy analysis. A subject's regression outcome is missing if her CIN grade and HPV clearance at Week 36 cannot be determined. Also, any subject who undergoes an unscheduled excision or biopsy in which tissue sample was obtained after Dose 1 and before Week 36 will be considered a non-regressor regardless of the Week 36 result. Efficacy analyses using the mITT population will be conducted and will serve as sensitivity analyses regarding missing data.

8.16 SUBGROUP ANALYSES

Primary and secondary efficacy endpoints will be analyzed by history of exposure to prophylactic HPV vaccines.

8.17 INTERIM ANALYSIS

For reasons of futility (early evidence of poor efficacy of VGX-3100) or safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

Group-level unblinded (VGX-3100, Placebo) summaries and analyses of efficacy will be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. Long-term follow-up data will continue to be collected for all subjects with remaining visits through the final Week 88 visit. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and all other efficacy endpoints corresponding to the cervix and the Week 36 visit on which to make decisions regarding the VGX-3100 program, while still gathering secondary and exploratory endpoint and safety data through the final Week 88 visit. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance, b) the secondary

endpoint of histopathologic regression, c) the secondary endpoint of virologic clearance, d) the secondary composite endpoint of histopathologic regression to normal and virologic clearance, e) the secondary endpoint of histopathologic regression to normal, and f) the secondary endpoint of histopathologic non-progression. None of these summaries or analyses will be provided if the total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group relative to this total count is less than 3% for a given summary/analysis. Also, items a) through f) are planned to be produced in the order in which they are listed, but as there are intersecting endpoints among these items, items among b) through f) will not be produced if the difference in total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group is 0, relative to any preceding item in the set. The group-level unblinded (VGX-3100, Placebo) production of the summaries and analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), PPD, which has already been providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded with respect to subject treatment assignment throughout the trial. The type I error of 0.05 will not be adjusted for this procedure.

9 DATA COLLECTION, MONITORING AND REPORTING

9.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that

have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

9.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. This retention period may be superseded by applicable regulatory requirements (e.g. minimum of 25 years for Health Canada). The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

9.4 SAFETY AND QUALITY MONITORING

9.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group; no formal interim analysis will be performed for this purpose. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full

DSMB review and ad hoc statistical analyses. The DSMB charter will define the membership, responsibilities and procedures for the meeting.

9.4.2 PATHOLOGY ADJUCATION COMMITTEE

All histology slides (i.e. cervical biopsies or surgical excision tissue) will be read by a Pathology Adjudication Committee (PAC) to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion.

9.4.3 CLINICAL MONITORING

Clinical Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
    - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
    - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Assure that the study facilities continue to be acceptable
    - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

10 ETHICS

10.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2 INSTITUTIONAL REVIEW BOARD OR INSTITUTIONAL ETHICS COMMITTEE (IRB/IEC)

The investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/IEC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/IEC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/IEC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

10.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

11 PROTECTION OF HUMAN SUBJECTS

11.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

11.2 COMPLIANCE WITH IRB/IEC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator must be provided to Sponsor.

11.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

11.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

11.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Product used in this study however will be asked to complete a participant diary card during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

11.6 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the sponsor in all participating countries and is fully supporting the study. Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted.

13 PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

14 REFERENCES

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15 APPENDIX

15.1 APPENDIX A: GUIDELINES FOR COLPOSCOPY, BIOPSY, AND SURGICAL EXCISION

Colposcopy Procedure

It is recommended that all study colposcopies performed after informed consent be according the procedures recommended by the American Society of Colposcopy and Cervical Pathology (ASCCP):

1. Use warm, clean water to lubricate the vaginal speculum. Avoid other lubricant substances which could obscure results.
2. If the vaginal walls are lax, a lateral vaginal sidewall retractor aligned perpendicular to the speculum may facilitate visualization.
3. Examine the cervico-vaginal secretions and remove any excess mucus from the cervix with saline-soaked cotton swabs.
4. Obtain any required specimens required for cytology and HPV testing.
5. Using low-power magnification (5x to 10 x) inspect the cervix for obvious areas of abnormalities.
6. Swab or spray the cervix with 3-5% acetic acid. Reapply every 2-3 minutes during the examination.
7. Use the green or blue filter to examine blood vessels. Increase magnification (15x)
8. Identify the distal and proximal boarders of the transformation zone.
    a. The inner border is the entire 360-degree circumference of the squamocolumnar junction
        i. If the junction is proximal to the external os, in the canal, use a cotton-tipped applicator to pry either the anterior lip up or the posterior lip down or use an endocervical speculum
        ii. If the junction is not visualized in its entire circumference, the colposcopy is deemed inadequate
    b. The distal limit of the transformation zone may be identified by finding the most distal crypt openings or nabothian follicles in the lips of the cervix and drawing an imaginary line connecting these landmarks
9. Inspect the entire new squamocolumnar junction and detect and evaluate any abnormal areas.
10. Evaluate the upper third portion of the vagina.
11. Lugol or Schiller's solution may be applied to further define previously identified lesions.

Cervical Biopsies

Endocervical Curettage

ECC is to be performed using a kervorkian curette or equivalent instrument. Rotate and scrape the curette 360° in the endocervical canal and use a cytobrush to remove the specimen. Deposit the specimen onto a Telfa pad before depositing in the specimen vial containing 10% neutral buffered formalin solution and labeled with the subject identification (SID) number.

Ectocervical Biopsies

Ectocervical biopsies should only be performed prior to Week 36 if disease progression is suspected. Only the suspect lesion should be biopsied in that circumstance.

If the subject is eligible for 4 quadrant biopsy at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the subject's ID number and the quadrant number according to the figure below.
2. Perform and record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform colposcopic directed biopsies from all quadrants.
4. Multiple biopsies can be obtained of a lesion at the discretion of the investigator but must be uniquely labeled
5. If a quadrant is free of lesions, obtain a random biopsy at the squamocolumnar junction in that quadrant at 2, 4, 8, or 10 o'clock.
6. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

Figure 1 – Biopsy Quadrant Numbers

Surgical Excision

For subjects undergoing surgical excision at the Week 36 visit, the following procedure should be followed:

1. Label each specimen vial containing 10% neutral buffered formalin solution with the SID number and the specimen type.
2. Record colposcopy findings from each quadrant according to the following categories
    a. Negative (no lesion present)
    b. Low Grade (e.g. pale acetowhite lesion on or off the squamocolumnar junction
    c. High Grade (e.g. dense acetowhite lesion often with mosaic pattern or punctation)
    d. Suspicion of invasive cancer
    e. Invasive cancer
3. Perform the LEEP or CKC per usual practice.
4. Specimen should be marked at 12 o'clock with suture or gentian violet ink for purposes of orientation
5. Prepare the biopsy specimen vials for shipment according to the Laboratory Manual.

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TITLE

Protocol Approval Page

SECTION 1: CLINICAL TRIAL PROTOCOL INFORMATION	
Protocol #:	HPV-301
Full Protocol Title:	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
Protocol Version #:	Version 5.0
Protocol Version Date: (ddMmmyyyy)	20 November 2019

SECTION 2: AUTHOR SIGNATURE

I wrote the protocol listed above and confirm that the content is complete and accurate.

[redacted]

[redacted] Date (ddMmmyyyy)

[redacted]

SECTION 3: APPROVAL SIGNATURES

My signature indicates that I have reviewed and approve the content of the protocol listed above.

[redacted] [redacted] Date (ddMmmyyyy)

[redacted] [redacted] Date (ddMmmyyyy)

[redacted] [redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

[redacted] [redacted] Date (ddMmmyyyy)

[redacted]

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[redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

[redacted] Date (ddMmmyyyy)

Protocol Administrative Memo (PAM) Signature Page

HPV-301

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

PAM # 1

Date: 10Sep2018

Written by:

[redacted] Date (DDMMMYYYY)

Reviewed and Approved by:

[redacted] MSN, CRNP, MBA [redacted] Date (DDMMMYYYY)

[redacted] MD, Ph.D. [redacted] Date (DDMMMYYYY)

Protocol Administrative Memo (PAM) # 1

PAM Date: 10SEP2018

To

HPV-301

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

Protocol Version: 4.0

Protocol Version Date: 29 March 2018

Sponsored by:

Inovio Pharmaceuticals, Inc.

IND #: 13683

EudraCT #2016-002761-63

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted] _____ [redacted] _____

Date

Inovio Pharmaceuticals, Inc.

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

I have read and understood this Protocol Administrative Memo (PAM) #1 and will incorporate it as part of the protocol. I will provide a copy of this PAM to the Institutional Review Board or Independent Ethics Committee (IRB/IEC) overseeing the conduct of the trial.

The signature of the Principal Investigator (PI) constitutes the PI's acknowledgement of, and agreement with, this PAM and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature: _____

_____ _____
Printed Name of Principal Investigator Date (DDMMMYYYY)

Site Number: _____

Site Name: _____

Item 1: Clarification of Section 6.1.1 Screening Evaluations

The current protocol reads as below:

*Additionally, Investigators may discuss with the Sponsor on a case-by-case basis the screening of subjects with abnormal cytology findings (**i.e.** HSIL or ASC-H with or without local HPV-16 or 18 genotype results) obtained as part of standard of care.*

It should be read:

*Additionally, Investigators may discuss with the Sponsor on a case-by-case basis the screening of subjects with abnormal cytology findings (**e.g.,** HSIL or ASC-H with or without local HPV-16 or 18 genotype results) obtained as part of standard of care.*

This memo is being provided to clarify that screening based on abnormal cytology findings is not limited to HSIL or ASC-H. A subject with any abnormal Pap smear cytology finding (including LSIL, ASCUS) with or without HPV typing may be eligible for screening upon written approval from the Medical Monitor.

Protocol Administrative Memo (PAM) # 2
PAM Date: 29APR2019

To

HPV-301

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

Protocol Version: 4.0

Protocol Version Date: 29 March 2018

Sponsored by:

Inovio Pharmaceuticals, Inc.

IND #: 13683

EudraCT #2016-002761-63

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted] _____ [redacted] _____

Inovio Pharmaceuticals, Inc.

Date

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. The changes do not affect the overall design, safety, or quality of the trial. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

I have read and understood this Protocol Administrative Memo (PAM) #2 and will incorporate it as part of the protocol. I will provide a copy of this PAM to the Institutional Review Board or Independent Ethics Committee (IRB/IEC) overseeing the conduct of the trial.

The signature of the Principal Investigator (PI) constitutes the PI's acknowledgement of, and agreement with, this PAM and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature: _____

_____ _____
Printed Name of Principal Investigator Date (DDMMMYYYY)

Site Number: _____

Site Name: _____

Item 1: Clarification of HIV Testing time window-within 45 Days of Day 0

Exclusion Criteria # 8a (Pages 22 and 49 of Protocol)

The current protocol reads as below:

a) History of or positive serologic test for HIV at screening (performed within 30 days prior to Day 0)

It should read:

*a) History of or positive serologic test for HIV at screening (performed within **45 days** prior to Day 0)*

This change will make the HIV testing window consistent with *Section 6.1.1 Screening Evaluations* of the Protocol which reads Serology (HIV Antibody, within 45 days of Day 0). This memo is being provided to clarify that serology HIV testing must be completed within 45 Days of Day 0.

Item 2: Clarification of Body Mass Index (BMI) calculation

The protocol does not currently specify whether to calculate stratification BMI based on screening measurements or Day 0 measurements. BMI should be calculated using height and weight measurements taken at Day 0 prior to dosing.

Sites are encouraged to calculate BMI manually using the below kg/m^2 formula, to calculate BMI for the determination of the stratification group within YPrime at Day 0.

$$BMI = weight\ (kg) / [height\ (m)]^2$$

or if using pounds and inches

$$BMI = 703 \times weight\ (lbs) / [height\ (in)]^2$$

Item 3: Clarifications to Procedures for Documenting Pregnancy During Study

Section 7.1.9:

The current protocol reads as below:

> *All pregnancies that occur from the time of **first screening procedure** through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.*

It should read:

*All pregnancies that occur from the time of **first study treatment** through the follow up visits must be reported. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.*

This memo is to update the pregnancy reporting time frame for those participants that become pregnant while participating in the trial. The protocol had erroneously reflected that pregnancies occurring following the first screening procedure will be followed through outcome, however, this would require the Investigator to follow pregnancies even for subjects that are not eligible for the study and are considered screen failures. It is not the Sponsor's intent to collect information regarding pregnancy outcome for subjects that are not exposed to Investigational Product.

Item 4: Clarifications to Section 8, Statistical Analysis Plan

Section 8.1:

The current protocol reads as below:

*Other **secondary** analyses concern safety and humoral and cellular immunological measures, and association of **Immunoscores and efficacy**. Exploratory analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, virology, other microRNA (miRNA) profiles, and DNA methylation profile and efficacy, and patient-reported outcomes.*

It should read:

*Other secondary analyses concern safety and humoral and cellular immunological measures. **Exploratory** analyses concern tissue immunological measures, durability of clearance of HPV-16 and/or HPV-18 infection from cervical tissue, effect of HLA type on efficacy, association of colposcopy, cytology, virology, other microRNA (miRNA) profiles, and DNA methylation profile and efficacy, patient-reported outcomes, and **association of Immunoscores and efficacy.***

This memo is to clarify the association of Immunoscores and efficacy is an exploratory objective.

Section 8.10:

The current protocol reads as below:

*Post-baseline cellular and humoral responses will be compared between treatment groups using a difference in medians and associated exact non-parametric 95% CI. Increases from baseline in interferon-γ ELISpot response magnitudes and in CD8+ / CD137+ PBMCs Perforin+ results and HPV E6 and E7 titers from ELISA at **Weeks 8, 15 and 36 visits** will be evaluated.*

It should read:

Post-baseline cellular and humoral responses will be compared between treatment groups using a difference in medians and associated exact non-parametric 95% CI. Increases from baseline in interferon-γ ELISpot response magnitudes and in CD8+ / CD137+ PBMCs Perforin+ results and HPV E6 and E7 titers from ELISA at ***Weeks 15 and 36*** *visits will be evaluated.*

This memo is to clarify that immunogenicity assessments will be conducted post-baseline at Weeks 15 and 36. Week 8 was removed to make this section consistent with other protocol sections that refer to post-baseline immunogenicity assessments only at Week 15 and 36 visits.

Section 8.11.2:

The current protocol reads as below:

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

It should be disregarded, as there are no safety laboratory post-baseline measurements, and therefore this section is not applicable.

Section 8.14

The current protocol reads as below:

As an exploratory endpoint, patient reported outcomes among subjects who receive VGX-3100 will be compared between those with excision versus those without excision, based on PRO endpoints. This comparison will utilize the median endpoint or the proportion of subjects with endpoints and associated Wilcoxon rank-sum test or Pearson chi-square test/Fisher's exact test, for continuous responses and categorical responses, respectively.

The mITT population will be used for PRO analyses.

It should read:

As an exploratory endpoint, patient reported outcomes will be compared between treatment arms, based on PRO endpoints. Median changes from baseline for the SF-36 and EQ-5D-5L responses and median days of worsened quality of life for the Week 40 Quality of Life questionnaire will be analyzed using exact non-parametric 95% confidence intervals for the differences in medians. The proportion of subjects who report a worsened quality of life for the Week 40 Quality of Life questionnaire will be analyzed using a 95% Miettinen and Nurminen confidence interval for the difference in proportions.

In addition, the Week 36 and beyond outcomes will be summarized according to those with excision versus those without excision.

The mITT population will be used for PRO analyses.

This memo is to provide further clarity and specification of these analyses.

Item 5: Clarification to referencing Tables 4 and 5: Minimally Required Procedure at Week 36

The current protocol indicates that Table 5 and 6 reference "Minimally Required Procedures at Week 36", however the actual table numbers showing the minimally required procedures at Week 36 are Table 4 and 5. These tables are references throughout the protocol in the following sections:

Study Design

Schedule of Events Footnotes

Section 1.3.2 Potential Risks of Study Participation

Section 2.3 Safety Monitoring Plan

Section 6.2.10 Week 36

Section 6.13.1 Ectocervical Biopsies

Item 6: Clarification to Appendix: Ectocervical biopsy Section. 4 Quadrant Biopsy:

Appendix:

The current protocol reads as below:

3. Perform colposcopic directed biopsies from all quadrants with lesions.

It should read:

3. Perform colposcopic directed biopsies from all quadrants.

Study participants qualifying for 4 quadrant biopsies should have biopsies collected from all four quadrants regardless of visible lesion being present.

Protocol Administrative Memo (PAM) # 3
PAM Date:26Mar2021

To

HPV-301

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

Protocol Version: 5.0

Protocol Version Date: 20Nov2019

Sponsored by:

Inovio Pharmaceuticals, Inc.

Investigational New Drug Application (IND) #: 13683

EudraCT #: #2016-002761-63

Medical Monitor Approval Page

Medical Monitor Signature:

DocuSigned by:
[redacted]

Date (ddMmmyyyy)

Inovio Pharmaceuticals, Inc.

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

The Principal Investigator's (PI's) signature constitutes the PI's acknowledgement of, and agreement with, this PAM and provides the necessary assurances that this clinical trial will be conducted in accordance with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), local legal and regulatory requirements, and all stipulations of the Protocol.

Principal Investigator Signature:

_____

Principal Investigator Printed Name (first and last)

_____ _____

Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Medical Monitor has been updated from [redacted], M.D., Ph.D. to [redacted], M.D.

The HPV-301 Protocol Version 5.0 currently states:

On Page 2 of 94:

Medical Monitor: [redacted], M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc.

The HPV-301 Protocol Version 5.0 should state:

On Page 2 of 94:

Medical Monitor: [redacted], M.D.
[redacted]
Inovio Pharmaceuticals, Inc.