COVER PAGE

Official Title:	REVEAL 2, A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly (IM) 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
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REVEAL 2

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

HPV – 303

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. IND #13683

EudraCT #: 2018-004114-17

Version 4.1

01Jun2022

FINAL

REVEAL 2: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA™ 5PSP FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE CERVIX

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Short Title: REVEAL 2 Trial (Randomized Evaluation of VGX-3100 and Electroporation for the Treatment of CervicAl HSIL)

Biological Product: VGX-3100

Protocol Number: HPV-303

Sponsor: Inovio Pharmaceuticals, Inc.

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Date (ddMmmyyyy)

CONFIDENTIAL

Summary of Changes

The following is a list of protocol changes organized categorically and secondarily in order of appearance from HPV-303 Protocol version 3.0 dated 15 November 2018 to Protocol version 4.1 dated 01 June 2022. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol. These are deemed to be non-significant. The discrepancies between the Protocol version 3.0 and Protocol Synopsis version 3.0 have been corrected in Protocol Version 4.1.

1. The primary population to which the primary objective will be applied has been changed from "all subjects" to "subjects defined as biomarker-positive at baseline," as identified by microRNA (miRNA) profiling performed from peripheral blood prior to dosing with VGX-3100 (Section 6.10). This change has been made in order to define a population of patients in whom VGX-3100 is more likely to be efficacious as defined by the pr ..n ..en point of regression of cervical HSIL and clearance of HPV-16/18.
2. The protocol has been revised to remove 4-quadrant biopsy as a potential procedure at Week 36 throughout the protocol.
3. Stopping Rules (Criteria for Pausing of Study) added to Data Safety Monitoring Board Charter version 3.0.
4. Update to acceptable contraception methods in Protocol Synopsis, Inclusion Criteria and Section 4.1, Inclusion Criteria. A footnote has been added to clarify that use of condoms or condoms and spermicide are not acceptable forms of contraception.
5. Update to Table 1: Schedule of Events and Sections 6.1.1, 6.1.2, and 6.4.12, Method of collection for cervical di ..ne™ samples. Text was changed to update the method of collection of cervical digene™ samples from swabs to brushes at Screening, Day 0, Weeks 15, 28, and 36.
6. Clarification of previous footnote "K" for Table 1: Schedule of Events. The footnote has been updated to indicate that a biopsy is only done at the Screening visits.
7. Clarification of previous footnote "M" for Table 1: Schedule of Events. The footnote has been updated to indicate that 4-quadrant biopsies will not be completed at Week 36.
8. Clarification of Section 3, Study Design and Endpoints and Section 8.7, Randomization and Blinding. 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.
9. Clarification of Section 3, Study Design and Endpoints. 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.
10. Clarification of the definition of Responder and Non-Responder in Section 3.1.4, 8.5.1 and 8.5.9. The definition of non-responder was clarified to comprise subjects who undergo excision, or subjects whose cervix is biopsied, at any time between their initial dose of study drug and the Week 36 endpoint tissue collection.

11. Clarification of HPV clearance result to Table 4 in Section 3.1.4 and Tables 6 and 7 in Section 3.2.
12. Clarification of Exclusion Criteria 3 in Section 4.2, Exclusion Criteria. The text has been updated to correspond with Exclusion Criteria 3 in the Clinical Protocol Synopsis.
13. Clarification of Exclusion Criteria 7 in Section 4.2, Exclusion Criteria. The text has been updated to correspond with Exclusion Criteria 7 in the Clinical Protocol Synopsis.
14. Clarification of Exclusion Criteria 12 in Section 4.2, Exclusion Criteria. The text has been updated to correspond with Exclusion Criteria 12 in the Clinical Protocol Synopsis.
15. Clarification of Section 6.1.1, Screening Evaluations. Text has been updated that Serology testing must be completed and negative within 60 days of Day 0.
16. Clarification of Section 6.1.1, Screening Evaluations. [redacted]
17. Clarification of Section 6.1.2, Week 40 (Study Co nclusion). Whole blood and serum samples are not obtained at Week 40 as indicated in Table 1, Schedule of Events. "Whole blood and serum for immunology" has been removed from the text.
18. Clarification of Section 6.4.3, Height and Weight. The text w s clarified to include that height and weight should be collected at Screening and on Day 0, Weeks 4 and 12, and that the BMI at Day 0 will be used to determine BMI Stratum for randomization.
19. Clarification of Table 13: Grading Scale for Injection Site Reactions in Protocol Section 6.9, Assessment of Injection Site Reactions. Daily activity is defined for the Injection Site Reactions table.
20. Clarification of Section 8.5 3, Planned I rim Analysis. Language was added to this section to explain that group-level unblinding summaries and analyses may be produced once the primary endpoint data are com leted for all subjects, if deemed necessary.
21. Clarification of Section 8.5.10.4, Vital Signs. The summary will be performed on the Safety population instead of the mITT population.
22. Clarification of Section 9 5.3, Compliance with Good Clinical Practice. The text has been updated to define GCP regulati ns as including ICH, ISO, and local regulations.
23. Clarification of Section 11, Source Documents. All prescription and nonprescription medications taken within 8 weeks prior to entry must be recorded on the CRF as stated in Section 6.12, Concomitant Medications/Treatment.
24. Clarification of Section 17, Appendices. Appendix A was updated to remove the procedure for collecting 4-quadrant biopsies at Week 36.

Administrative Changes:

25. Administrative Change to Inclusion Criteria 5 in the Clinical Protocol Synopsis. The text has been updated to correspond with Inclusion Criteria 5 in Section 4.1, Inclusion Criteria.
26. Administrative Change to Exclusion Criteria 3 in Section 4.2, Exclusion Criteria. The text has been updated to correspond with Exclusion Criteria 3 in the Clinical Protocol Synopsis.

27. Administrative Change to Section 5.3, CELLECTRA™ 5PSP device. A statement was added for informational purposes indicating that CELLECTRA™ 5PSP device is CE Marked in the European Union.
28. Administrative Change to Section 6.4.13, Colposcopy and Cervical Biopsies and Section 6.4.15, Unscheduled Biopsies. The guidelines for Colposcopy and Surgical Excision is in Appendix A.
29. Administrative Change to Section 7.2, Adverse Events (AEs), and Section 7.11, Procedure for Reporting Pregnancy During the Study. The additional information on pregnancy reporting is referenced there.

PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

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

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol 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 Date (DDMMYYYY)

_____

Printed Name

Site Number: _____

Site Name: _____

EudraCT #: 2018-004114-17

TABLE OF CONTENTS

Clinical Protocol Synopsis

Protocol Title: REVEAL 2, A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly (IM) 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
Protocol Number: HPV-303
Trial Phase: 3
Estimated Number of Trial Centers and Countries/Regions: Approximately 50 study centers in approximately 9 countries
Formulation: VGX-3100 delivered with CELLECTRA™ 5PSP Electroporation Device
Trial design: Prospective, Randomized, Double-blind, Placebo-Controlled
Criteria for evaluation: **Hypothesis**: Among baseline biomarker-positive women, three 6 mg doses of VGX-3100 (DNA Plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered by intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA™ 5PSP to adult women with histologically confirmed high-grade squamous intraepithelial lesions (HSIL), Cervical Intraepithelial Neoplasia, (CIN2, 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] **Primary Objective**: Among baseline biomarker-positive women, determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18. **Primary Endpoint**: Proportion of baseline biomarker-positive women with no evidence of cervical HSIL on histology sample 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. Among i) baseline biomarker-positive women and ii) all women, 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 (i.e., 40 weeks). 1b. Incidence and severity of all adverse events including Serious adverse events (SAEs) (e.g., Serious unexpected serious adverse reaction (SUSAR), Unexpected adverse device effect (UADE) and other unexpected AEs) for the duration of the study (through Week 40 visit).
2. Among all women, determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18.	2. Proportion of all women with no evidence of cervical HSIL on histology sample and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit.
3. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by histopathologic regression of cervical HSIL.	3. Proportion of women with no evidence of cervical HSIL on histology sample at Week 36 visit.
4. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by virologic clearance of HPV-16 and/or HPV 18.	4. Proportion of women with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit.
5. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal.	5. Proportion of women with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e., no evidence of CIN1, CIN2 or CIN3) on histology sample at Week 36 visit.
6. Among i) baseline biomarker-positive women and ii) all women, 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.	6. Proportion of women with no evidence of LSIL or HSIL (i.e., no evidence of CIN1, CIN2 or CIN3) on histology sample and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit.
7. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by histopathologic non-progression.	7. Proportion of women with no progression of cervical HSIL to cervical carcinoma from baseline on histology sample at Week 36 visit.
8. Among i) baseline biomarker-positive women and ii) all women, describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations.	8. Proportion of women who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (oropharynx,

Secondary Objectives	Associated Secondary Endpoints
	vagina and intra-anal) at Week 36 Visit compared to baseline.
9. Among i) baseline biomarker-positive women and ii) all women, determine the humoral and cellular immune response of VGX-3100 compared with placebo at post dose 3 and Week 36 visit as assessed relative to baseline.	9a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15 and 36 visits 9b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15 and 36 visits 9c. Flow Cytometry response magnitudes at baseline and Week 15 visits.

Exploratory Objectives	Associated Exploratory Endpoints
[redacted]	

Study Design

Trial Treatment: 6 mg (1 ml) VGX-3100 Intramuscular injection followed by EP with the CELLECTRA™ 5PSP device given at Day 0, Week 4 and Week 12
Efficacy Assessment: The primary endpoint for the Phase 3 study (HPV-303) is based upon the results of the Phase 2b study (HPV-003) and the Phase 3 study (HPV-301). Given that HPV persistence is an important factor in the clinical progression of cervical dysplasia and also based upon the findings of the secondary objective of the HPV-003 study, the responder definition for the HPV-303 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16 and HPV-18. Regression of cervical HSIL will be determined by histopathological assessment of cervical tissue, which is considered the definitive method for diagnosis of cervical dysplasia. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36. Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28 and 36. Also, if there is residual tissue in the paraffin block after his ogic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be colle ted for testing of HPV-16 and /or HPV-18. Vaginal, oropharyngeal, and optional intra-anal samples will be obtained 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.
Immunogenicity Assessment: Humoral and cell mediate immun 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. [redacted]
Safety Assessment: Based upon the HPV-003 results, the risk of HSIL progression to cancer or recurrence of HSIL is considered low and comparable to the rates observed post-LEEP/CKC [1]. The long-term follow-up planned for this HPV-303 stud will include safety, cytology and HPV-16 and/or HPV-18 testing up to 7 months following the last dose of Study Treatment. A Data Safety Monitoring Board (DSMB) wi l review safety data and histopathological regression results. The DSMB will be charged with adv sing the Sponsor if there appears to be a safety issue and if it appears that the proportion o he subjects with histopathologic regression in the VGX-3100 group is unacceptably low compared to the pla ebo group. No formal interim analysis will be performed.
Trial Population: Women 18 years of age and older will be recruited in this multi-center global trial. VGX-3100 is being developed as a non-surgical therapeutic option for the treatment of the precursor to cervical cancer, precancerous cervical HSIL, and the underlying pathogenic HPV-16 and/or HPV-18 infection.

Inclusion Criteria:

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

1. Women aged 18 years and above that meet 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 Pathological Adjudication Committee (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(s) 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 Pot ntial (WOCBP) is willing to use a contraceptive method with failure rate of less than 1% per year[a] when used onsistently 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 mode of sexual activity;
        - Intrauterine device or intrauterine system;
        - Male partner steriliz tic n 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 Electrocardiogram (ECG) or screening ECG with no clinically significant findings, as judged by the investigator.

[a] Use of condoms alone or condoms with spermicide does not have a failure rate of <1% per year and is therefore not an acceptable form of contraception.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from enrollment or continuation 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 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 60 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 60 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) 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 (locally treated ano-genital malignancy and superficial skin cancers 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 (except HPV-301 REVEAL 1) 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.

Schedule of Events

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 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)
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
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
HIV Antibody Testing	X [q]											
Blood immunologic samples [f]	X [q]	X				X			X [g]		X	
Cervical digene brushes [i, j]	X [q]	X							X	X	X	
ThinPrep™ [h, i]	X [q]	X				X			X	X	X	
Colposcopy [k]	X [l, q]	X							X	X	X	X
Ectocervical biopsy [m]	X [q]											
Surgical excision [m]											X [n]	
OP rinse, vaginal swabs, intra-anal swabs [o]		X									X	
Inject VGX-3100/Placebo		X		X			X					
Post treatment assessment		X	X	X	X	X	X	X [p]	X			
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X
Distribute Participant Diary Card (PDC)		X		X			X					
Review PDC			X		X	X		X [p]				

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

[b] Complete physical examination (PE) mandatory at screening and study discharge (Week 40), otherwise targeted physical assessment as determined by the investigator or per subject complaints unless signs or symptoms dictate the need for a complete PE;

[c] Screening vital signs must include a measured height and weight. Height and weight will be collected on Day 0, Weeks 4 and 12;

[d] Screening safety procedures includes 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum Albumin, serum glucose, serum ALT, serum CPK and urinalysis performed within 60 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;

[redacted]

[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 lesions before colposcopic examinations for the Screening and Week 36 visits;

[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. In the absence of paraffin-embedded or fresh tissue, unstained slides will be required in addition to H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 by excision (e.g. LEEP, LLETZ, CKC);

[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 assessment of [redacted] as well as HPV testing;

[o] Please refer to the Laboratory Manual for specific information regarding biological sample collection;

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

[q] Results and activities performed as part of the screening process in the HPV-301 trial can be used as qualifying historical information to satisfy screening activities for HPV-303 provided that they were assessed within the required timeframes for HPV-303 screening.

1 INTRODUCTION

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the ano-genital area and aero-digestive 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 [2]. In the US alone, approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type [3, 4]. Up to 13,000 women in the US alone are diagnosed with cervical cancer each year, with an estimated 4,120 deaths annually in year 2017 [5]. 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 [6],[7].

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) [8]. Over time, typically years, cervical HSIL can progress to invasive cancer of the cervix [9, 10]. 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.

1.2 BACKGROUND INFORMATION

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 [11]. 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 did not respond to vaccination, must currently 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 [12]. 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.

1.3 PRODUCT DEVELOPMENT OVERVIEW

1.3.1 INVESTIGATIONAL PRODUCT

VGX-3100 contains plasmids that encode HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using Inovio's proprietary SynCon™ (synthetic consensus) 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. The initial formulation of VGX-3100 was water for injection with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage and was administered by the CELLECTRA™ 2000 device. The frozen formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled HPV-003 study of VGX-3100 (frozen formulation) followed by EP in the treatment of high-grade cervical dysplasia, cervical HSIL associated with HPV-16 and/or HPV-18. HPV-003 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, frozen formulation) or the placebo arm, respectively. All subjects received treatment on Day 0, Week 4 and Week 12. All subjects repeated cervical biopsy or LEEP of the cervix at Week 36 to assess efficacy defined as regression of high grade CIN by histology. 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 CIN 1 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. T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 demonstrated an acceptable safety profile when administered intramuscularly followed by electroporation.

In preparation for the Phase 3 program, a buffered refrigerated (2–8° C storage) formulation of VGX-3100 was developed using a saline sodium citrate (SSC) solution. The refrigerated formulation requires administration using the next generation device, the CELLECTRA™ 5PSP. This refrigerated formulation of VGX-3100 was first administered to 17 subjects in a Phase 1 clinical trial, HPV-101. Roughly half the healthy volunteers in the HPV-101 study, received three 6 mg IM doses of VGX-3100 (refrigerated formulation) followed by EP. Based upon an analysis of the data, the refrigerated formulation was determined to be 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.

1.3.2 CELLECTRA™ DEVICE DEVELOPMENT

CELLECTRA™ 2000 & 5PSP are electroporation (EP) devices. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electrical field at the injection site which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [13, 14]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced immunogenicity by 10 to 100-fold [15, 16]. 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 [13]. 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) [14, 15].

In preparation for the Phase 3 program, a next generation device, CELLECTRA™ 5PSP, was created to address ergonomic functionality and automate the delivery of VGX-3100 and EP. The technology

differences between the CELLECTRA™ 2000 and CELLECTRA™ 5PSP design do not affect the intended mechanism of EP on the activity of VGX-3100 and will not present any new risks. The device design change does not affect the indications for use, operating principle, energy type, or sterilization specifications. The CELLECTRA™ 5PSP has been approved for investigational use in the US with VGX-3100 and is being used in a Phase 3 clinical study HPV-301, titled "A Prospective, Randomized, Double-blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly (IM) 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".

Together, VGX-3100 and the CELLECTRA™ device represent an integrated product designed as a non-surgical treatment for HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18. Therefore, the refrigerated formulation of VGX-3100 and the CELLECTRA™ 5PSP device were chosen to progress into Phase 3 clinical development. Full preclinical design verification testing and a non-significant risk device functionality study have been completed prior to the start of Phase 3. The intent is to support that the dimensional changes, change to the ergonomics of the patient user interface and injection method result in the CELLECTRA™ 5PSP de ice design meeting its safety and performance specifications. The mechanical process f administration has changed from manual to automatic, but the overall administration of VGX-3100 followed by electroporation is the same as in the CELLECTRA™ 2000. Inovio's device experience demonstrates hat delivery of its proprietary electroporation pulses into muscle immediately following injection f DNA plasmids (including VGX-3100) is well-tolerated in humans and no significant safety ssues have been identified [1], [14], [16]. For further information concerning the 5PSP de ice please refer to the User Manual and the Investigator's Brochure.

1.3.3 RATIONALE

A total dose of 6 mg VGX-3100 DNA has been selected or this study based on previous human experience with both the frozen and refrigerated form ns f VGX-3100, preclinical data with VGX-3100 and DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV- 101 studies. In the HPV-001 trial, the 6 m dose was delivered IM followed by EP, which showed trends toward higher response rates and magni des of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 2) without significant safety issues [14].

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 een 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 HPV-003. The results obtained in HPV-003 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 [1].

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

1.4 POTENTIAL RISKS AND BENEFIT

1.4.1 POTENTIAL RISKS

Risks associated with VGX-3100 for the treatment of high-grade cervical dysplasia are 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 potential risk is the delay of surgical intervention of the high-grade cervical dysplasia and possible missed diagnosis of an occult early invasive cervical cancer for the VGX-3100 non-responders or placebo recipients, who do not spontaneously regress. 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. To mitigate these potential risks 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.

A Data Safety Monitoring Board (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 of progression of the cervical HSIL and the risk of harboring an undiagnosed occult early invasive cervical cancer. Secondary to the potential risk of progression to cancer during the course of the trial described above, all subjects with the suggestion of residual disease will undergo excisional therapy (e.g. CKC, LEEP, LLETZ) at Week 36 as part of the efficacy assessment. In the HPV-003 study, the percentage of subjects with micro-invasive cancer 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 that reported under standard of care settings [17]; never the less, all subjects will undergo excision at Week 36 to ensure no evidence of occult progression.

For further information concerning the risks associated with VGX-3100 and the CELLECTRA™ 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.4.2 POTENTIAL BENEFITS

Subjects that participate in the study may potentially see benefit from the investigational treatment if it proves efficacious. The close follow-up required by this study will also enable careful monitoring of the existing precancerous lesion(s). Overall, the study results will provide new information that may benefit other subjects in the future.

1.5 RISKS FOR CURRENT TREATMENT

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) [12].*

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.

2 OBJECTIVES AND PURPOSE

Among baseline biomarker-positive women, determine the efficacy of VGX-3100 compared to placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18.

2.1 HYPOTHESIS

Among baseline biomarker-positive women, 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 histopathologic 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 STUDY DESIGN AND ENDPOINTS

The HPV-303 study design is based upon the HPV-003 and HPV-301 study designs and results. It will also provide confirmation of the initial Phase 3 study, HPV-301, with regard to histologic regression of cervical HSIL and clearance of the underlying HPV 16/18 infection. HPV-303 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 the CELLECTRA™ 5PSP device in adult

women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18. 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.

To be eligible for the study, subjects at least 18 years age and above the age of consent must agree 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 the PAC in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for randomization, 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.

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 among biomarker-positive women, assuming, based upon HPV-301 study results, that the true proportion of subjects whose lesion(s) regress and whose HPV-16/18 clear is 66% and 15% for VGX-3100 and placebo, respectively, and that the proportion of biomarker-positive women is 33%. Biomarker positivity in this context is defined as being predicted to exhibit lesion regression concomitant with HPV-16/18 clearance after interrogation of a pre-defined microRNA (miRNA) signature in subject plasma which is assessed prior to the administration of VGX-3100 or placebo. Those subjects who are not predicted to exhibit lesion regression and HPV-16/18 clearance based on this signature prior to dosing with VGX-3100 or placebo are considered biomarker-negative.

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) 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. Each country will receive a group of sequential allocation numbers.

3.1 PRIMARY OBJECTIVE

Among baseline biomarker-positive women, determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18.

3.1.1 PRIMARY ENDPOINT & EFFICACY ASSESSMENT

The primary endpoint for HPV-303 is based upon the results of HPV-003 and HPV-301 and is identical to the primary endpoint of the HPV-301 study, but for a biomarker-positive population. 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 HPV-003 study, the responder definition for the HPV-303 primary endpoint determination will take into consideration both histological regression of cervical HSIL and clearance of high-risk HPV-16/18. The composite endpoint of histologic regression and virologic clearance will be primary in the HPV-303 study, and histologic regression will be a secondary endpoint.

3.1.2 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. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36by excision (e.g., LEEP, LLETZ, CKC).

3.1.3 VIROLOGIC ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28 and 36, for all subjects. 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, intra-anal, and oropharyngeal samples will be obtained 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.

3.1.4 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 4) 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 after their initial dose and before the Week 36 endpoint tissue collection time frame. 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 for the primary endpoint, the subject must have:

1) An acceptable histology specimen at the Week 36 time frame, which is interpretable by the independent PAC

2) An acceptable HPV ThinPrep™ sample at the Week 36 time frame, with an associated valid HPV-testing result.

A responder is defined as a subject with:

- No histologic evidence of cervical HSIL
- No evidence of HPV-16 or HPV-18
- The subject must not have had an unscheduled excision or biopsy sample obtained between initial dose and the Week 36 evaluation.

To be qualified as a non-responder any subject with:

- Histologic evidence of cervical HSIL, or
- Evidence of HPV-16 or HPV-18, or
- An excision or biopsy sample obtained between initial dose and the Week 36 evaluation, or
- No Week 36 visit sample/result

Table 4: Definition of Composite Regression and Clearance 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 visit[b] **AND** Subject in whom 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 with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in whom an excision or biopsy sample 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 rem val sample determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the timeframe determines the HPV clearance endpoint.
[c] Excludes ECC-only samples.

3.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Among i) baseline biomarker-positive w men and ii) all women, evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 5PSP.	1a. Inci ence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (i.e., 40 weeks). 1b. Incidence and severity of all adverse events including Serious adverse events (SAEs) (e.g., Serious unexpected serious adverse reaction (SUSAR), Unexpected adverse device effect (UADE) and other unexpected AEs) for the duration of the study (through Week 40 visit).
2. Among all women, determi 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.	2. Proportion of all women with no evidence of cervical HSIL on histology sample and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit.
3. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by histopathologic regression of cervical HSIL.	3. Proportion of women with no evidence of cervical HSIL on histology sample at Week 36 visit.
4. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by	4. Proportion of women with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit.

Secondary Objectives	Associated Secondary Endpoints
virologic clearance of HPV-16 and/or HPV-18.	
5. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal.	5. Proportion of women with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e., no evidence of CIN1, CIN2 or CIN3) on histology sample at Week 36 visit.
6. Among i) baseline biomarker-positive women and ii) all women, 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.	6. Proportion of women with no evidence of LSIL or HSIL (i.e., no evidence of CIN1, CIN2 or CIN3) on histology sample and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit.
7. Among i) baseline biomarker-positive women and ii) all women, determine VGX-3100 efficacy compared to placebo as measured by histopathologic non-progression.	7. Proportion of women with no progression of cervical HSIL to cervical carcinoma from baseline on histology sample at Week 36 visit.
8. Among i) baseline biomarker-positive women and ii) all women, describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations.	8. Proportion of women 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 compared to baseline.
9. Among i) baseline biomarker-positive women and ii) all women, determine the humoral and cellular immune response of VGX-3100 compared with placebo at post dose 3 and Week 36 visit as assessed relative to baseline.	9a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Weeks 15 and 36 visits 9b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15 and 36 visits 9c. Flow Cytometry response magnitudes at baseline and Week 15 visits.

3.2.1 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, for all subjects. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 by excision (e.g., LEEP, LLETZ, CKC).

3.2.2 VIROLOGIC ASSESSMENT

Cervical cytology samples will be obtained to characterize HPV infection at screening, Day 0 (prior to dosing) and Weeks 8, 15, 28 and 36, for all subjects. 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, intra-anal, and oropharyngeal samples will be obtained 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.

3.2.3 DEFINITION OF RESPONDER AND NON-RESPONDER

Table 5: 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 whom 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 whom an excision or biopsy sample 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 determines the histology endpoint.
[c] Excludes ECC-only samples

Table 6: 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 whom 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 or carcinoma at Week 36 visit **OR** Subject in whom an excision or biopsy sample 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 determines the histology endpoint.
[b] Excludes ECC-only samples.

Table 7: 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 whom 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 whom an excision or biopsy sample 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 determines the histology endpoint.
[b] Excludes ECC-only samples

Table 8: Definition of Secondary Composite 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 whom 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 whom an excision or biopsy sample 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 determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the timeframe determines the HPV clearance endpoint.
[c] Excludes ECC-only samples

Table 9: 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 whom an excision or biopsy sample[b] was NOT obtained[c] between initial dose up to Week 36 visit	Subject with evidence of HPV-16 or HPV-18 at Week 36 visit **OR** Subject in whom excision or biopsy sample 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 determines the histology endpoint. The most recent HPV clearance result prior to tissue removal within the timeframe determines the HPV clearance endpoint.
[b] Excludes ECC-only samples
[c] This applies only to the cervical clearance endpoint.

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

[redacted]

Exploratory Objectives	Associated Exploratory Endpoints
[redacted]	

3.4 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses to the 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 be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (Screening).

[redacted]

3.5 SAFETY ASSESSMENT

The safety monitoring plan is based upon the Phase 2b HPV-003 study results and the design of the Phase 3 HPV-301 study. Longer term follow-up data of approximately 1.5 years after the last dose has been collected and reported in the HPV-003 Clinical Study Report. Longer term safety data will also be collected through approximately 1.5 years after the last dose in the HPV-301 Phase 3 study. The HPV-303 study has been designed to follow participants for approximately 7 months following their last dose of study treatment to serve as an independent second pivotal demonstration of the efficacy of VGX-3100.

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 HPV-003, 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. Over the course of the entire 88 week study, sinusitis was statistically more commonly observed in the VGX-3100 group (10%) than in the placebo group (0%), but resolved without sequelae.

Histology is the gold standard for the diagnosis of cervical HSIL. Therefore, the definitive histopathologic assessment in the Phase 2b study was determined by an independent blinded Pathology Adjudication Panel, comprised of experienced cytopathologists from independent medical centers in the US, who are also adjudicating the HPV-301 study. This will enable the highest certainty of the diagnosis for study entry with the exclusion of individuals with carcinoma and also enable a consistent and accurate histologic endpoint evaluation.

Cervical disease will be monitored 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. The increased frequency of monitoring is designed to afford an even wider margin of safety and an opportunity to explore predictors of efficacy. 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 s owly, typically over years, which makes close, active follow-up possible. All subjects will undergo excisional therapy by . EEP, LLETZ or CKC at Week 36 as part of the efficacy assessment [18].

Importantly, investigators in the HPV-303 stud will be chosen o ly if they are experienced in the management of cervical cancer as was the case in the HPV-003 study. Phase 3 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical b opsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy w l be classified as a non-responder in the efficacy analysis as outlined in Table 4. T ese measures shou minimize the risk of progression of cervical HSIL and the risk of harboring an undia nosed occult early vasive cervical cancer. The frequency of close monitoring by experienced investigat rs should minimize the risk of cancer progression on the study what is expected with standard of care.

An independent Data and Safety Monitoring Board (DSMB) will also provide safety oversight as is being done for the HPV-301 study. 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.

3.5.1 SUMMARY OF LONG TERM FOLLOW UP DATA FROM PHASE 2B STUDY

In HPV-003, cervical tissue samples were 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. 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 micro-invasive cancer was found based on confirmed cases in larger surgical excision samples in subjects who had no evidence of invasive cancer by initial biopsy in the VGX-3100+EP arm was 1.8%, (2/114 with specimens) and across both arms was 1.3% (2/155 with specimens), which is consistent with that reported under standard of care settings [19].

In the HPV-003 study, all subjects were scheduled to be followed for approximately 1 year (Week 88) after the histopathologic assessment of the primary endpoint. 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). Investigators were instructed to perform a LEEP/CKC in 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 10).

Cytology and HPV-16/18 clearance from the cervix was 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 10 which summarizes the HPV and cytology results following Week 36.

Table 10: HPV-003 HPV and Cytology Results at Weeks 36, 62 and 88, mITT Population

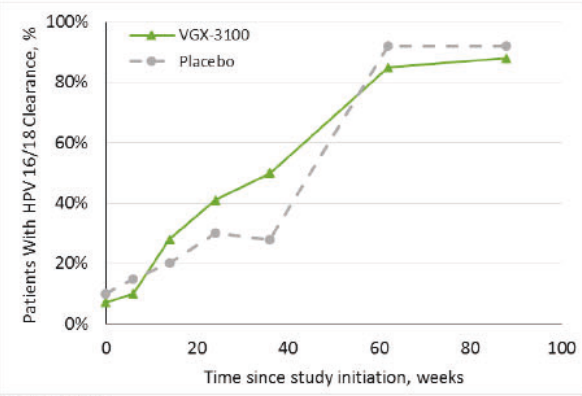
		VGX-3100		Placebo	
Week	Test[a]	LEEP/CKC[b] %(n/N)	Biopsy[c] %(n/N)	LEEP/CKC %(n/N)	Biopsy %(n/N)
36	HPV	41% (19/46)	63% (36/57)	29% (6/21)	29% (5/17)
36	Pap	NA	NA	NA	NA
62	HPV	89% (50/56)	82% (42/51)	96% (27/28)	82% (9/11)
62	Pap	93% (52/56)	100% (51/51)	93% (26/28)	82% (9/11)
88	HPV	89% (48/54)	89%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

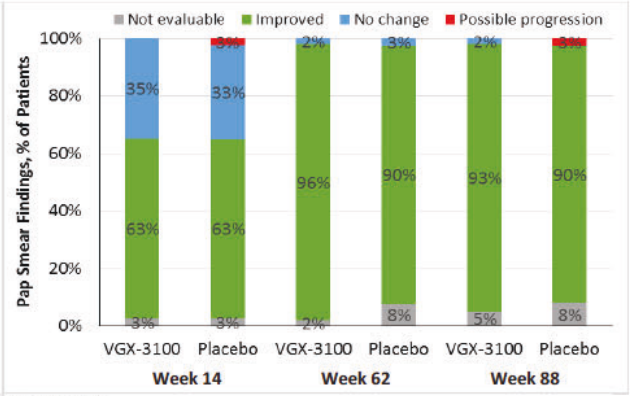
a.



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-1′ /18 clearance at Week 62 was 89% (50/56) for VGX-3100 post-LEEP/CKC, 82% ‚42/51) for VGX-3 00 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, ″ (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 underlyin , cervical HPV-16′18 infection by Week 62 without meaningful changes through Week 88, and without meaningful differences between groups.

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 nd 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 ecurrences 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 t ` VGX-3100 treated group at Week 88. Overall, these virologic clearance findings support that study subjects had no increased risk of recurrence in comparison to standard of care.

Cytology (mITT population) post-Week 36 are described as follows: Improvement compared to study entry for Pap smear 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).

Improvement compared to study entry for Pap smear 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 10). Based upon the Phase 2b results, the risk of recurrence of cervical dysplasia and the risk of persistent High Risk HPV infection under these clinical trial conditions is lower than the rates observed post-LEEP/CKC in clinical practice. For example, Xi et al. showed that in a prospective cohort of women with HPV-16 who participated in the ASCUS and LSIL triage study (ALTS), 6.0% (12/201) subjects had a recurrence of CIN 2 or CIN 3 at 12 months post-LEEP [20]. In a very large retrospective cohort study (n = 3,273 women treated for CIN2, CIN3, or AIS) Katki et al found, in the subgroup of patients who had an AGC, ASC-H, OR HSIL+ p etreatm t screening result (n = 1,461 women), a CIN2+ recurrence at 12 months post-treatment of 6.1% in wom n treated for CIN2 and 9.8% in women treated for CIN3 [21]. Nobbenhuis et al. have reported a rate of I igh Risk HPV persistence of 14% (26/181) at 12 months post-LEETZ [22], as did Moore et al with 12 months post-treatment (LEEP, cone, or laser ablation) persistence of: HR-HPV at 29.7% (260/874), HPV-16 at 14% (58/416), and HPV-18 at 11% (11/99) [23].

The collection of cytology and virology data f r an a onal year of follow-up after the removal of tissue at Week 36 was reassuring in that no significant recurrence of cytological or virological disease was noted. However, the removal of tissue at Week 36 did appear to obfuscate the differences between the treatment groups that were present at that time but normalized across groups after that visit presumably due to the removal of infected and/or dys lastic tissue. Assuming the longer term virologic and cytologic data collected in the companion HPV-301 Phase 3 stud are similar to what was seen in the HPV-003 Phase 2b study, the collection of virologic and/or cytol c data beyond the Week 36 primary endpoint visit would not be expected to yield significant results in t is companion Phase 3 study.

4 STUDY POPULATION

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 that meet 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(s) 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 rem ins after Screening biopsy;
10. Must meet one of the following criteria with respect to their rep oductive 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) are w illing to use a contraceptive method with failure rate of less than 1% per year[a] when used consistently and correctly from Screening until Week 36. The following methods are acce ɲ.b e
        - Hormonal contraception: either combi ed 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 e. / -vaginal intercourse when this is the subject's preferred mode of sexual activity;
        - Intrauterine device or intrauterine system;
        - Male partner sterilizat ˇ 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.

[a] Use of condoms alone or condoms with spermicide does not have a failure rate of <1% per year and is therefore not an acceptable form of contraception.

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 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;
6. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil™, 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. [illegible] emed clinically significant by the investigator 60 days prior to Day 0;
8. Immunosuppression as a result of underlying illnes or treatment inclu ing:
    a) History of or positive serologic test for HIV at screening (performed within 60 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, cyclophosp am de, 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 inter [illegible] wit s udy sessments or endpoint evaluation, or otherwise impact the validity of the study results.
    g) Subjects who are malnourished based on screening labs, medical history (e.g. clinically significant unintentional weight loss) and physical exam, as determined by investigator's clinical judgment
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 systemic treatment for malignancy within 2 years of screening (locally treated ano-genital malignancy and superficial skin cancers are allowed);

4.2 EXCLUSION CRITERIA (continued)

13. Presence of acute or chronic bleeding or clotting disorder that would contraindicate intramuscular (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 onsidering 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 preven 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 t e 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

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 safety follow-up assessments through study disc arge 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.

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), to 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). If these attempts to contact the subject are unsuccessful the subject can be considered as withdrawn from the study (i.e. lost to follow-up). If contact with the subject is re-established, the site should contact the Medical Monitor to discuss whether the 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.

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 blood samples collected as indicated in the Schedule of Events in 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.

The primary reason for a subject discontinuing further do ng 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, (including manner of de th if known)
- Subject voluntarily withdrew consent: The subject desired o withdraw from further participation in the study in the absence of an investiga or-determined me ical 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 rom participation: Investigator determined a medical need to withdraw the s oject. Investigator must consult the Sponsor's Medical Monitor before withdrawing a subject rom participation in the study.
- Protocol Deviation: T e 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 deviation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatment 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.

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

The active and placebo formulations to be used in this study are described in Table 11. Both Investigational Products (IPs) will be presented in clear glass cartridges and injected intramuscularly.

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

Table 11: 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 m . 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 n difference in appe rance between the active product and the placebo.

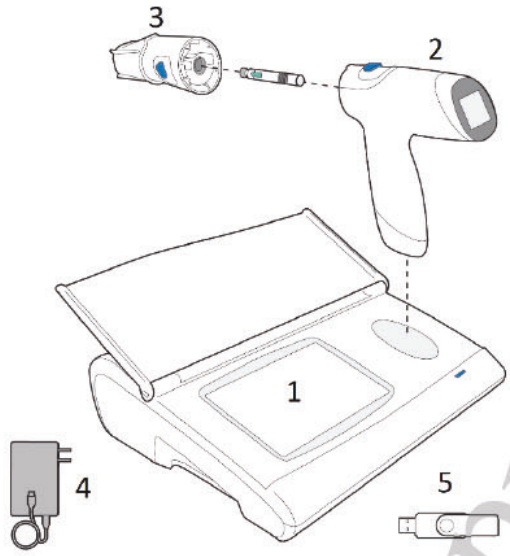
The investigator may request to unblind a subject's treatment assignment in case of an emergency or serious medical condition when knowledge of the study treatment is es ential for proper clinical management of the subject, as judged by the investigator. It is preferred, but n t required, that the investigator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

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

5.3 CELLECTRA™ 5PSP DEVICE

The investigational product/placebo will be delivered using the CELLECTRA™ 5PSP device. The CELLECTRA™ 5PSP device is CE Marked in the European Union. The device consists of five (5) main components (see Figure 2):

Figure 2: CELLECTRA™ 5PSP Base Station with Handset



1. 5PSP Base Station which serves as a charging dock for the Handset and can accept limited data inputs as well as store records.

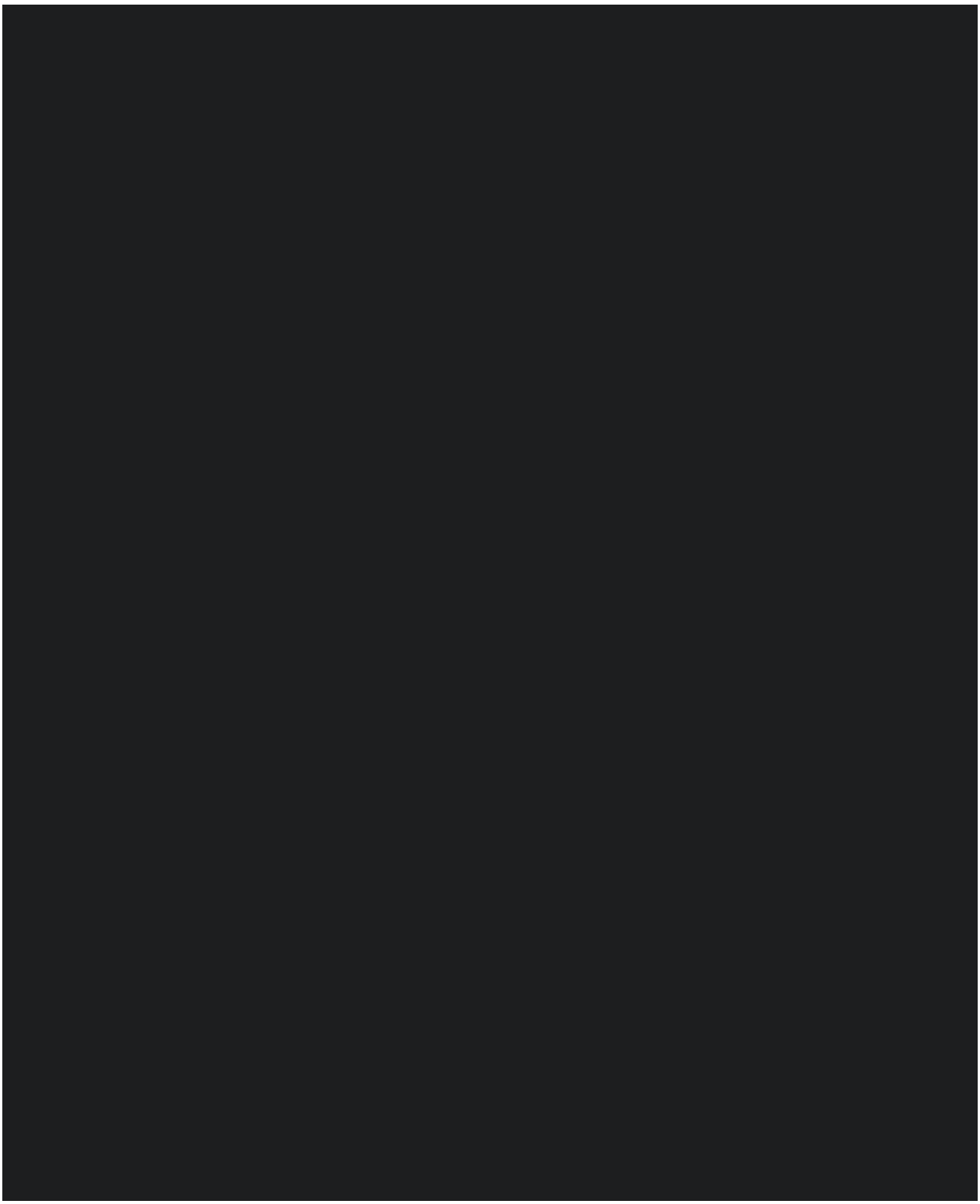
2. 5PSP Handset, a reusable handset which is battery powered and delivers the electroporation pulse pattern. The Handse accepts the disposable array.

3. 5PSP terile Sing.e Use Array which consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The ar y accepts a stanc rd, commercially available glass cartridge.

4. USB International Power Supply

5. Flash Drive

[redacted]



5.4 TREATMENT REGIMENS

The three-dose regimen of VGX-3100 appeared to be safe and well tolerated in the HPV-003 study, therefore all eligible subjects who consent to participate in the HPV-303 study will receive three 6 mg doses of VGX-3100 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. 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, concurrent with the positive testing for HPV-16/18.

5.5 PACKAGING AND LABELING

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-of . Both VGX-3100 and placebo labels will include, at minimum, the following information in Table 12:

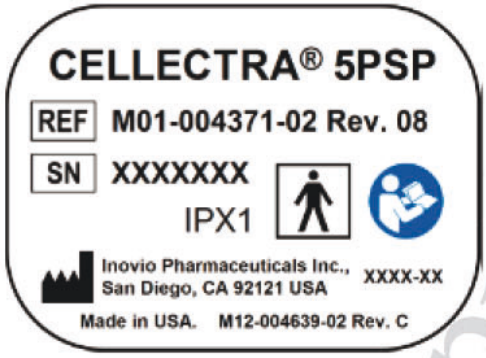
Figure 6: Examples of Device Labels (Base, Handset, Array):

Base Station

CAUTION:
Investigational device.
Limited by Federal (or United States) law to investigational use.

M12-002942-02 Rev. C

Handset



CAUTION:
Investigational device.
Limited by Federal (or United States) law to investigational use.

M12-002942-02 Rev. C

Array

5.6 HANDLING AND STORAGE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual. For the specific temperature guidelines for storing, please refer to the CELLECTRA™ 5PSP User Manual. 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 records 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.

5.7 PREPARATION AND DISPENSING

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 mus not be removed fr m 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. If the IP is not used within this time frame it must be discarded after reconciliation.

5.8 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of he CELLECTRA™ 5PSP are located in the CELLECTRA™ 5PSP User Manual. Users of the CELLECTRA™ 5PSP device must successfully complete training before using the device. Training will include review of the entire device User Manual as well as hands-on training. After training on the proper use of the CELLECTRA™ 5PSP device, the intended users at each site will be required to demonstrate their competency in its use to Inovio personnel 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.

5.9 INVESTIGATIONAL DRUG AND DEVICE ACCOUNTABILITY

5.9.1 INVESTIGATIONAL PRODUCT

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/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.

5.9.2 CELLECTRA™ 5PSP DEVICE

The site is responsible for maintaining the device and its accountabili logs. The device must have full traceability from receipt of the components through the device use, return of the device. The site must document acknowledgement of receipt and then notify Inovio upon eceipt of the device. This includes the content shipped and condition of the items upon r eip.

For each subject treatment, there must be record of each pro ct used for that subject, i.e. CELLECTRA™ 5PSP Base Station & Handset serial number, Array lot number and the study drug lot number. The used Array attachment must be disposed of in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN AND DESTRUCTION O INVESTIGATIONAL DRUG AND DEVICES

5.10.1 INVESTIGATIONAL PRODUCT

Upon completion or term ation 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. personal 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.

5.10.2 CELLECTRA™ 5PSP DEVICE

Upon completion or termination of Inovio's 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 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 must be granted by Inovio Pharmaceuticals, Inc., or its designee of the disposal,
- Ensure that proper procedures for disposal have been established and followed according to applicable local regulations, guidelines and institutional procedures,
- Appropriate records of the disposal have been documented.

6 STUDY PROCEDURES AND SCHEDULE

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. Results and activities performed as part of the screening process in the HPV-301 trial can be used as qualifying historical information to satisfy screening activities for HPV-303 provided that they were assessed within the required timeframes for HPV-303 screening. Participants will be consented for the HPV-303 trial and asked that their historical results be applied to HPV-303. All participants will be screen failed as part of HPV-301 regardless of participation in HPV-303.

Protocol waivers or exemptions will not be granted. Immediate safety concerns will be dealt with as deemed necessary by the investigator. Adherence to the study design requirements, as outlined in the Schedule of Events Table are essential and required for study conduct. Subject eligibility should be reconfirmed at every study visit.

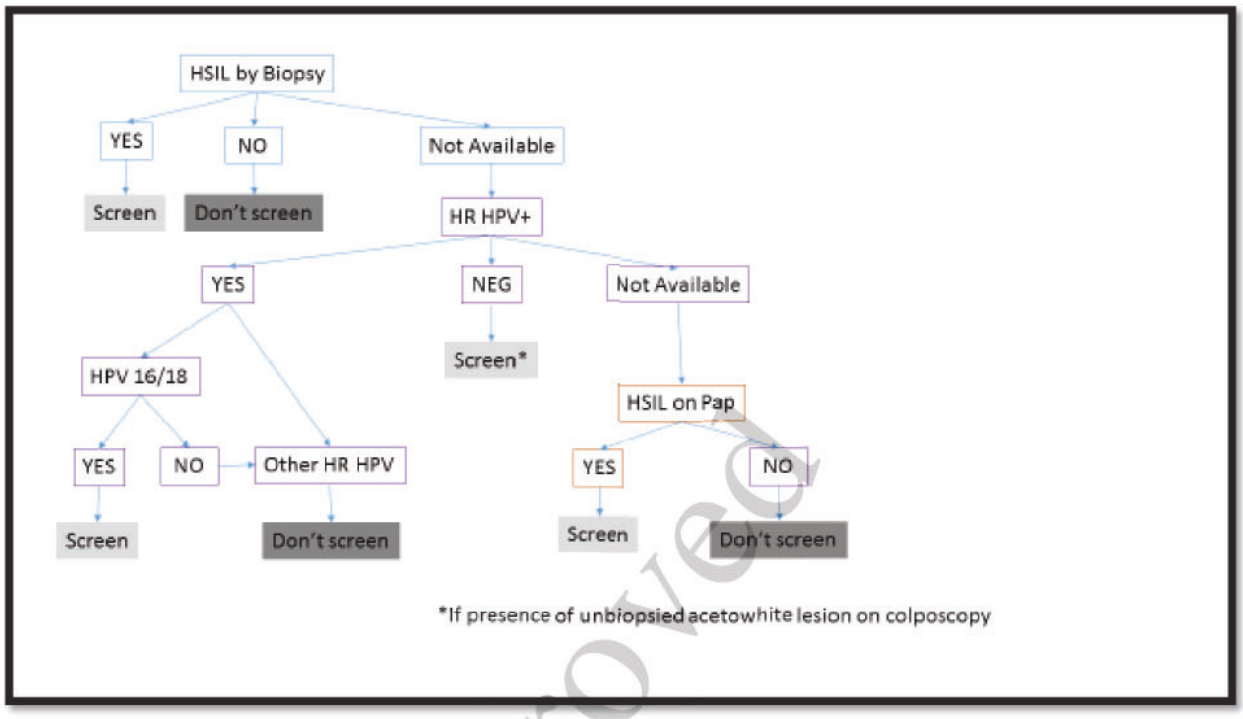
6.1 PROCEDURES BY VISIT

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 the PAC for evaluation prior to enrollment.

Figure 7 below illustrates the information in order of priority that could help in the identification of potential subjects for screening.

Figure: 7 Screening Priority Recommendations:



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 the PAC with HSIL consensus diagnosis) [redacted] f first study treatment (i.e. Day 0).

Biopsy specimens and colposcopy 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, a colposcopy should be performed, and an additional biopsy sample collected during screening. 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.

SCREENING VISIT

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 60 days prior to Day 0. All screening assessment values must be reviewed prior to study treatment assignment.

Results and activities performed as part of the screening process in the HPV-301 trial can be used as qualifying historical information to satisfy screening activities for HPV-303 provided that they were assessed within the required timeframes for HPV-303 screening and the subject provides consent.

- Signed informed consent
- Determination of eligibility per inclusion/exclusion criteria
- Demographics; including age, race/ethnicity and hand dominance
- Medical history; including concomitant medications review, history of prior cervical dysplasia, and pregnancy history
- Socio-behavioral assessment; including smoking history, exposure to second-hand smoke, alcohol intake history, recreational drug use and contraceptive use
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate)
- Complete Physical Examination (including height, weight and BMI measurements)
- digene™ cervical brush 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 cervical biopsy
- 12-lead ECG (within 60 days prior to Day 0)
- Baseline laboratory evaluations (includes CPK, hematology and serum chemistry, urinalysis) to be performed (within 60 days prior to Day 0);
- Serology (HIV Antibody, within 60 days of Day 0)
- [redacted]

6.1.2 STUDY EVALUATIONS AND PROCEDURES

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

DAY 0

The following evaluations will be performed at Day 0 prior to study treatment:

- Determination of eligibility per inclusion/exclusion criteria
- Randomization
- Targeted physical assessment
- Vital signs including weight

- Urine pregnancy test
- [redacted]
- 2 digene™ cervical brush 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 swab (if subject has consented to intra-anal sampling) for HPV testing
- Colposcopy
- Study treatment administration

The following evaluations will be performed on Day 0 post-t eatment:

- Post treatment adverse event and injection site reactio asse ment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)

****Please remember to download EP data from de ce within 24-48 hours of study treatment. ****

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 reatment injection assessment with the subject on the phone, the investigator or study personnel w l determine whether an office visit is needed for further evaluation)

WEEK 4 (±4 DAYS)

The following study evaluation will be perfo med at Week 4 prior to study treatment:

- Targeted physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect PDC for dose 1
- Study treatment will be administered

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

- Post treatment adverse event and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC

****Please remember to download EP data from device within 24-48 hours of study treatment. ****

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 Week 4 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)

WEEK 8 (±4 DAYS)

The following study evaluation will be performed during the visit:

- Targeted physical assessment
- Vital signs
- 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)
- [redacted]

WEEK 12 (±4 DAYS)

The following study evaluation will be performed on Week 12 prior to study treatment:

- Targeted physical assessment
- Vital signs including weight
- Urine pregnancy test
- Study treatment will be administered

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

- Post treatment adverse event and injection site reaction assessment within a minimal of 30 minutes after study treatment
- Distribute PDC

****Please remember to download EP data from device within 24-48 hours of study treatment. ****

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 Week 12 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.)

WEEK 15 (± 1 WEEK)

The following study evaluations will be performed at Week 15:

- Targeted physical assessment
- Vital signs
- Post-treatment injection site reaction assessment
- Urine pregnancy test
- [redacted]

- 2 digene™ cervical brush 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
- Collect PDC

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 brush 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 to assess for possible disease progression

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)
- Urine pregnancy test
- [redacted]
- 2 digene™ cervical brush 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 swab (if subject has consented to intra-anal sampling) for HPV testing
- Colposcopy
- Surgical excision to be used for histopathologic assessment

WEEK 40 (STUDY CONCLUSION)

The following study evaluations will be performed on Week 40 ± 2 weeks:

- Complete Physical Examination
- Vital signs
- Socio-behavioral assessment (change in smoking alcohol intake or recreational drug use from baseline)
- Urine pregnancy test
- Colposcopy

****Study Conclusion****

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and Good Clinical Practice (GCP). Qualified study personnel will meet with prospective study participants, 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 or subject's legally acceptable representative is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject or subject's legally acceptable representative. 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 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. Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the eCRF.

Subjects meeting eligibility criteria listed in the protocol will be randomized by a computer-generated allocation schedule.

6.4 SAFETY EVALUATIONS

6.4.1 PHYSICAL EXAMINATION

A complete 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, lymph nodes, 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.

6.4.2 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

6.4.3 HEIGHT AND WEIGHT

Height and weight will be collected at Screening and on Day 0, Weeks 4 and 12.

The BMI at the Day 0 visit will be used to determine the BMI stratum for randomization.

6.4.4 MEDICAL HISTORY

All relevant past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems (as judged by the investigator). The medical history will include

a) Any prior history of CIN diagnosed – with diagnosis date(s) and respective CIN level(s),
b) If treated previously for CIN, the respective treatment type(s) and date(s).

6.4.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-behavioral assessment, including self-reported smoking history, history of exposure to second-hand smoke, alcohol intake history, recreational drug use, contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening, Weeks 36 and 40. Socio-behavioral assessmen s ll b performed to document any change from Screening.

6.4.6 LABORATORY EVALUATIONS

At Screening, blood samples will be taken to be te ed fo 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:
- Albumin
- Glucose
- Serum glut nic-pyruvic transaminase (SGPT)/Alanine aminotransferase (ALT)
- Blood urea nitro e B N)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

6.4.7 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.

6.4.8 DEMOGRAPHICS

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

- Dominant hand

6.4.9 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. A final pregnancy test will also be done at Week 40 to capture pregnancy status at study completion.

6.4.10 ECG

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for at least 10 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.

6.4.11 PARTICIPANT DIARY CARD (PDC) SUBJECT SELF EVALUATION

Subjects will be provided and trained on 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 the 8 -14 day post-dose phone call and at the 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.

6.4.12 PAP SMEARS AND HPV TESTING

Pap smears will be obtained using ThinPrep™ test kits at screening, Day 0, Weeks 8, 15, 28 and 36. They will be sent to 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, Weeks 15, 28 and 36) where multiple cervical samples are collected, the two digene™ cervical brushes will be collected prior to the ThinPrep™ sample. [redacted]

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. Non-cervical swabs (vaginal and intra-anal) along with an oropharynx rinse will be collected at specified visits for HPV typing.

6.4.13 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 and 36. An unscheduled colposcopy may be performed at the discretion of the investigator if there is suspicion of disease worsening or progression.

6.4.14 ECTOCERVICAL BIOPSIES

Ectocervical biopsies are required at Screening to confirm eligibility.

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. For this reason, if biopsies are obtained prior to the Week 36 visit, 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.

6.4.15 UNSCHEDULED BIOPSIES

In the event an unscheduled biopsy is performed prior to the Week 36 visit, the subject will be classified as a non-responder in the efficacy analyses. The subject may 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.

6.5 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.

6.6 MANAGEMENT OF ANXIETY AND PAIN DUE TO EP PROCEDURE

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.

6.7 ASSESSMENT OF LABORATORY ABNORMALITIES

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

6.8 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

The injection site will be assessed by study personnel prior to and of 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.

6.9 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale in Table 13.

Table 13: 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
***Daily activity = Impact lasting ≥ 24 hours

6.10 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENT

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.

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.

[redacted]

[redacted]y

[redacted]

6.12 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.

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)

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered. All medications should be recorded in the appropriate sections of the subject's eCRF.

6.13 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

As a requirement for inclusion in the HPV-303 study investigators will only be chosen if they are experienced in the management of cervical cancer. HPV-303 investigators are instructed to perform additional, ad hoc colposcopic exams and cervical biopsies if they suspect potential disease progression. Subjects that undergo an early unscheduled biopsy will be classified as a non-responder in the efficacy analyses. These precautions should minimize the risk of progression of cervical HSIL. The increased frequency of close monitoring by experienced investigators should minimize the risk of cancer progression and the risk of an underlying misdiagnosis of invasive cancer.

7.2 ADVERSE EVENTS (AES)

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 7.11 for additional information on pregnancy reporting.
- All AEs that occur from when the informed consent is obtained onwards and throughout the duration of the study, including the follow-up off study drug p riod will be re rded as an AE.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth ex raction, transfusion) performed; the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions or labora tory abnormalities present or detected before the Screening visit that do not worsen.
- Situations where an untoward medica occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience dmissions).
- 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 RF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.3 SERIOUS ADVERS EVENT (SAES)

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:
    - allergic bronchospasm requiring intensive treatment in an emergency room or at home,
    - blood dyscrasias or convulsions that do not result in inpatient hospitalization,
    - the development of drug dependency or drug abuse or
    - development of a malignancy
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

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 interru te temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk o eath from the event as it occurred. This does not include an event that might have led to death if it had oc urred with greater severity.
- Complications that occur during hospitaliza ons are AEs. I 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 7.15.3.

7.4 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (A R) is any noxious and unintended responses to a medicinal product related to any dose; for which a causal rel tions ip 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 adverse event or ADR is considered unexpected if it is not listed in the applicable product information (Investigator's Brochure, Protocol, or User Manual) or is not listed at the specificity or severity which is consistent with the risk information provided. The Sponsor will assess each serious adverse drug reaction 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 patient population, or a major safety finding from a study conducted in animals.

7.5 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.

7.6 ASSESSING SEVERITY (INTENSITY)

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

The investigator will grade laboratory AEs with respect to the following levels of severity as defined in the document "Toxicity Grading Scale" for applicable patient populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)
- Death (Grade 5)

The investigator will grade clinical AEs or SAEs (based on discussions with study participants) in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

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.

7.7 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a possible, probable or definite relationship to the administration of the IP and/or the device. An AE may also be assessed as not related to the investigational product 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 EP 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 study subject, the circumstances surrounding the event, 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 related to drug or related to device or related to both drug and device (i.e. indiscernible) by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment (drug or device or both drug and device) 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 EP;
- 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.

7.8 ABNORMAL LABORATORY VALUES

Laboratory abnormalities are usually not r corded as AEs or ´ AEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead tɔ IP interruption oʻ discontinuation must be recorded as an AE, as well as an 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

Severity will be assessed as detailed in Section 7.6.

7.9 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 Sponsor.

7.10 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.

7.11 PROCEDURE FOR REPORTING PREGNANCY DURING THE STUDY

Subjects who are pregnant or expect to become pregnant prior to Week 36 of the study will be excluded from participation in the study. Should a subject become pregnant after randomization, she will not be given any further treatments with the investigational product. A Pregnancy Form will be completed by the investigator and submitted to the sponsor study team and Medical Monitor 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 7.15.3. The investigator will also report this event to the IRB/EC 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 IP. 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.

7.12 METHODS AND TIMING OF COLLECTION 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 40.

The sources of AEs cover:

- 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).
- Symptoms spontaneously reported by the subject.
- Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.

- 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.

7.13 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

7.14 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse Events of special interest (AESI) are the adverse events deemed related to VGX-3100/Placebo delivered with the CELLECTRA™ device 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 (e.g., malaise, chills, fatigue), including generalized pruritus

Sites will inform the Sponsor via the method described in Section 7.15.2 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.15 ADVERSE EXPERIENCE (AE) REPORTING

To assure the safety of the participants, information about all AEs (see Section 7.2), 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.

7.15.1 STUDY REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the EDC system. The Study Report will analyze and summarize all adverse events 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 will be collected and summarized for the entire study period

7.15.2 STUDY REPORTING PERIOD FOR ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) (see Section 7.14) 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]

7.15.3 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 report this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the IRB/IEC 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 7.4 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.5 (Unanticipated [Serious] Adverse Device Effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of all SUSAR reports. The investigator should notify the IRB/EC 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.

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 patient 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/EC 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.

7.16 NOTIFICATIONS 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 drug reaction 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 7.5 and 7.4). Results of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

7.17 REPORTING OF DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint/device deficiency is defined as any written, electronic, or oral communication that alleges deficiencies or inadequacies of the device or components related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device or components after it is released for distribution within the clinical investigation. All product complaints that meet this definition (with the exception of SAEs requiring 24 hr reporting) must be reported to the Sponsor with 10 days of discovery.

Device deficiencies include malfunctions, use errors 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 or marketed.

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] or fax to [redacted].

7.18 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/EC, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal Statistical Analysis Plan is contained in the sections that follow.

8.2 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 the Week 36 timeframe. The primary hypothesis is that VGX-3100 will be superior to placebo regarding the proportion who achieve the primary endpoint among baseline biomarker-positive women. Secondary efficacy analyses involve regression to CIN1 and complete regression, clearance of HPV-16 and/or HPV-18 infection from cervical and non-cervical tissue, and non-progression of cervical lesions. Other secondary analyses concern safety, humoral and cellular immunological measures. [redacted]

8.3 STATISTICAL HYPOTHESES

The true treatment effect on the primary endpoint is $\delta = p_V - p_P$, where p_V and p_P denote the true biomarker-positive population probabilities of the primary endpoint for VGX-3100 and Placebo, respectively. The primary hypothesis of superiority is: H_0: $\delta \leq 0$ *vs*. H_1: $\delta > 0$. There are no other formal hypotheses.

8.4 ANALYSIS POPULATIONS/DATASETS

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 biomarker-positive 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 received.

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

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

$$H_0: \delta \leq 0 \; vs. \; H_1: \delta > 0.$$

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the method of Miettinen and Nurminen [17]. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI exceeds zero.

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. 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 primary efficacy endpoints. Table 4 provides details for the definition of the primary endpoint response.

The ITT biomarker-positive population will be primary for the analysis of efficacy in this study. Missing data will be considered as non-regressors (failures) for the ITT efficacy analysis. Efficacy analysis using the mITT population will also be conducted and will serve as sensitivity analyses regarding missing data. The PP population will also be used for a supportive analysis. An additional analysis on the PP population will utilize the Week 36 timeframe result regardless of excision or biopsy performed before the Week 36 time frame, thus serving as a sensitivity analysis regarding early intervention. Additional analyses will be performed on all subjects regardless of biomarker status.

8.5.2 ANALYSIS OF THE SECONDARY ENDPOINTS

8.5.2.1 Efficacy

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

Table 5 through Table 9 provide details for the definitions of the secondary endpoint responses.

The ITT biomarker-positive population will be used for the analyses of these endpoints. Missing data will be considered as non-regressors (failures) for the ITT efficacy analyses. Efficacy analyses using the mITT population will also be conducted and will serve as sensitivity analyses regarding missing data. The PP population will also be used for supportive analyses. Additional analyses on the PP population will utilize the Week 36 timeframe result regardless of excision or biopsy performed before the Week 36 time frame,

thus serving as sensitivity analyses regarding early intervention. Additional analyses will be performed on all subjects regardless of biomarker status.

8.5.2.2 Immunogenicity

Post-baseline cellular and humoral response magnitude will be compared between treatment groups using a difference in medians and associated non-parametric 95% CIs.

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. Valid samples for statistical analysis purposes will be those collected within 7 days of the specified visit. Baseline is defined as the last measurement prior to the first treatment administration.

The mITT biomarker-positive population will be used for immunogenicity analyses. Additional analyses will be performed on all subjects regardless of biomarker status.

8.5.3 SAFETY ANALYSES

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 [17]. 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.

Analyses and summaries will be performed on biomarker-positive subjects and on all subjects regardless of biomarker status separately.

8.5.4 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. Summaries will be performed on biomarker-positive subjects and on all subjects regardless of biomarker status separately.

8.5.5 BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic 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. Summaries will be performed on biomarker-positive subjects and on all subjects regardless of biomarker status separately.

8.5.5.2 Medical History

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT population. Summaries will be performed on biomarker-positive subjects and on all subjects regardless of biomarker status separately.

8.5.5.3 Prior Medications

Prior medications are those that were used before the start of the trial (prior to Day 0). Partial stop dates of prior 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 medications will be summarized with percentages by treatment arm, for the mITT population. Summaries will be performed on biomarker-positive subjects and on all subjects regardless of biomarker status separately.

8.5.6 PLANNED INTERIM ANALYSES

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.

Group-level unblinded (VGX-3100, Placebo) summaries and analyses may be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and key safety outcomes on which to make decisions regarding the VGX-3100 program while awaiting final database lock. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance and b) adverse events of progression to cervical cancer. Both will be performed on the biomarker-positive set of subjects and on all subjects. 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. 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.

8.5.7 SUBGROUP ANALYSES

Primary and secondary efficacy endpoints will be analyzed by history of exposure to prophylactic HPV vaccines.

8.5.8 MULTIPLICITY

Not applicable, there is one hypothesis that will be tested.

8.5.9 MISSING VALUES

Missing data will be considered as non-regressors (failures) for the ITT efficacy analyses. A subject's regression outcome is missing if the CIN grade and HPV clearance at the Week 36 time frame cannot be determined. Also, any subject who undergoes an unscheduled excision or biopsy in which cervical tissue sample is obtained after Dose 1 and before the Week 36 timeframe will be considered a non-regressor regardless of the Week 36 timeframe result.

Efficacy analyses using the mITT population will be conducted and will serve as sensitivity analyses regarding missing data.

8.5.10 EXPLORATORY ANALYSES

8.5.10.1 Efficacy

[redacted]

8.5.10.3 Concomitant Medications

Concomitant medications are those used during the course of the trial (on or after Day 0). Partial stop dates of 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 concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.5.10.4 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.

8.5.10.5 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.

8.6 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 among biomarker-positive women, utilizing the methodology described in Section 8.5.1, and assuming that the true proportion of subjects who achieve the primary endpoint is 66% and 15% for VGX-3100 and placebo, respectively, and that the proportion of biomarker-positive women is 33%. These proportions also incorporate missing data classified as non-regressors (failures) in accordance with the ITT analysis approach. The assumptions are based on the HPV-301 study results.

8.7 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. Randomization and blinding will avoid bias in the assignment of participants to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

9.2 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE (IRB/EC)

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/EC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/EC include the following:

- During the conduct of the study, submit progress reports to the IRB/EC as required, and request re-review and approval of the study at least once a year;
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects;
- If Sponsor notifies you about any reportable safety events notify the IRB/EC immediately;

- As required, obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or patient recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB/EC by the investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines;
- Maintain a file of study-related information (see study files) that includes all correspondence with the IRB/EC;
- Notify IRB/EC when study is completed (i.e. after the last study visit of the final study patient);
- After study completion (within 3 months is recommended) provide the IRB/EC with a final report on the study.

9.3 IBC APPROVAL AND REPORTING

Investigator will ensure responsibilities relevant to Institutional Biosafety Committee (IBC) approval and reporting if applicable per local regulations.

9.4 ADDITIONAL APPROVAL AND REPORTING

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. National Institutes of Health/Office of Science Policy) governing research that involves recombinant or synthetic nucleic molecules.

9.5 PROTECTION OF HUMAN SUBJECTS

9.5.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to enrollment 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 (see Section 6.2).

9.5.2 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.5.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

GCP regulations and guidelines include International Council of Harmonization (ICH) and International Organization for Standardization (ISO) and applicable local regulations.

9.5.4 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.

9.5.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the Investigational Product used in this study. 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.

9.5.6 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/EC 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). 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.

10 DATA COLLECTION, MONITORING AND REPORTING

10.1 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 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 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 all applicable laws, regulations or directives relating to privacy and data protection.

11 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. The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents related to this study.

A medical history and history of medications must be present in the source documents. All prescription and nonprescription medications taken within 8 weeks prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

11.1 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 their country and until there are no pending or contemplated marketing applications in their country 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 country requirements. The Sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

12 SAFETY AND QUALITY MONITORING

12.1 LONG TERM SAFETY FOLLOW-UP

Subjects will be followed for safety for 7 months after the last dose of VGX-3100. During this time they will be attending scheduled visits with qualified investigators to monitor their health and condition. The investigators have the ability to perform unscheduled biopsies if deemed necessary.

12.2 DATA SAFETY MONITORING BOARD

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.

12.3 PATHOLOGY ADJUDICATION 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 at least two pathologists independently in a blinded fashion.

12.4 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. Clinical site monitoring tasks will include but not be limited to the following 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/EC 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/EC,
    - Throughout the study, inspect all source documents to ensure they are attributable, legible, contemporaneous, original, accurate, and correct (ALCOAC),
    - 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.

13 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.

14 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).

15 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Adenocarcinoma-in-situ
AGC	Atypical Glandular Cell
ALCOAC	Attributable, legible, contemporaneous, original, accurate, and correct
ASC-H	Atypical Squamous Cells, cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CKC	Cold knife conization
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DNA	Deoxyribonucleic Acid
ECC	Endocervical Curettage
EP	Electroporation
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
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
ICF	Informed Consent Form
ICH	International Conference on Harmonization

IFN-γ	Interferon Gamma
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization of Standardization
ITT	Intent to Treat
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
MM	Medical Monitor
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PE	Physical Examination
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
TNF	Tumor Necrosis Factor
WOCBP	Women of Childbearing Potential

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17 APPENDICES

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 a d HPV test ng.
5. Using low-power magnification (5x to 10 x) inspect he 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. [illegible] 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 n[illegible]s alized in its entire circumference, the colposcopy is deemed inadequ[illegible]e
    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 app ied 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.

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, LLETZ 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.