Official Title:	**A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 Related Anal or Anal/Peri-Anal, High Grade Squamous Intraepithelial Lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in Individuals That Are Seronegative for Human Immunodeficiency Virus (HIV)-1/2**
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HPV-203

A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal, High grade squamous intraepithelial lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2

Sponsored by:
Inovio Pharmaceuticals, Inc.

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Medical Monitor Approval Page

Drug: VGX-3100

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Date

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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 (IRB/IEC) 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 International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

<Insert Principal Investigator Printed Name>	Date (dd/Mmm/yyyy)

Site Number: _____

Site Name: _____

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal High-Grade Squamous Intraepithelial Lesions, HSIL (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2
Protocol Number: HPV-203
Trial Phase: 2a
Estimated Number of Trial Centers and Countries/Regions: Approximately 5 study centers located in North America
Formulation: VGX-3100
Trial Design: Multi-center, single-arm, open-label phase 2 study
Criteria for Evaluation: To provide a treatment to regress anal or anal/peri-anal HSIL and clear the related HPV-16 and/or HPV-18 (HPV16/18) in individuals that are seronegative for HIV-1/2. **Research Hypothesis:** VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal HSIL[1], (AIN2[2], AIN3[3], PAIN2[4], PAIN3[5]) associated with HPV-16 and/or HPV-18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.
Dose of VGX-3100: 6 mg (1mL)
Administration: Intramuscular injection followed by EP
VGX-3100 Dosing Schedule: Day 0, Week 4 and Week 12 with one additional dose given to partial responders at Week 40
Study Duration: 88 Weeks
Primary Objective: Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18.
Primary Endpoint: Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL[6] on histology (i.e., collected via biopsy or excisional treatment)[7] and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue.

[1] High-grade Squamous Intraepithelial Lesion
[2] Grade 2 Anal Intraepithelial Neoplasia
[3] Grade 3 Anal Intraepithelial Neoplasia
[4] Grade 2 Peri-anal Intraepithelial Neoplasia
[5] Grade 3 Peri-anal Intraepithelial Neoplasia
[6] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.
[7] A treatment responder is defined as a subject with no histologic evidence of anal or anal/peri-anal HSIL and no evidence of HPV-16 or HPV-18 in anal lesion tissue and who did not receive non-study treatment of curative intent of intra-anal and/or peri-anal lesions. A treatment non-responder is defined as a subject with histologic evidence of anal or anal/peri-anal HSIL, adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma or a subject with evidence of HPV-16/18 in anal lesion tissue or a subject who received non-study treatment of curative intent of intra-anal and/or peri-anal lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC). 1b. **All** adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study (through the Week 88 visit)
2. Determine the **efficacy** of three doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL[8] on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
3. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue	3. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18[9] from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
4. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal tissue swab testing	4. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
5. Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue	5. Proportion of subjects with **no evidence** of anal or anal/peri-anal Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
6. Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL	6. Proportion of subjects with **no progression**[10] of anal or anal/peri-anal HSIL to carcinoma from baseline to histology (i.e. biopsies or excisional treatment) at the Week 36 visit
7. Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in size of peri-anal lesion(s) if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36	7. Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s), as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy

	photographic imaging at Weeks 36, 64, and 88 compared to the post-biopsy photographic image of the previous biopsy visit.
8. Determine the humoral and cellular immune response following dose 3 and additional time points compared to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline and the Weeks 15, 36, 64, and 88 visits 8b. Interferon-γ ELISpot response spot forming units (SFU) at baseline and the Weeks 15, 36, 64, and 88 visits 8c. Flow Cytometry response magnitude at baseline and Week 15 visit

[8] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.

[9] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.

[10] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16 and/or HPV-18	1. Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
2. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
3. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18	3. Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
4. Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples	4. Assessment of immunologic markers (e.g. CD8+ and FoxP3+ infiltrating cells). Additional assessments may include Granulysin, Perforin, CD137, CD103, and PD-L1 in intra-anal and/or peri-anal tissue as sample allows
5. Describe the **clearance** of HPV-16 and/or HPV-18 infection from non-anal anatomic locations	5. Proportion of subjects who have **cleared** HPV-16 and/or HPV-18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
6. Evaluate the effect of Human Leukocyte Antigen (HLA) type on **efficacy**	6. HLA (per-locus and per-allele basis) in conjunction with **histologic regression** of anal or anal/peri-anal HSIL at the Week 36 visit
7. Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression	7. HRA, cytology, and HPV test results and miRNA profile (baseline and at the Weeks 15 and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit

8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100	8. Patient reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose.

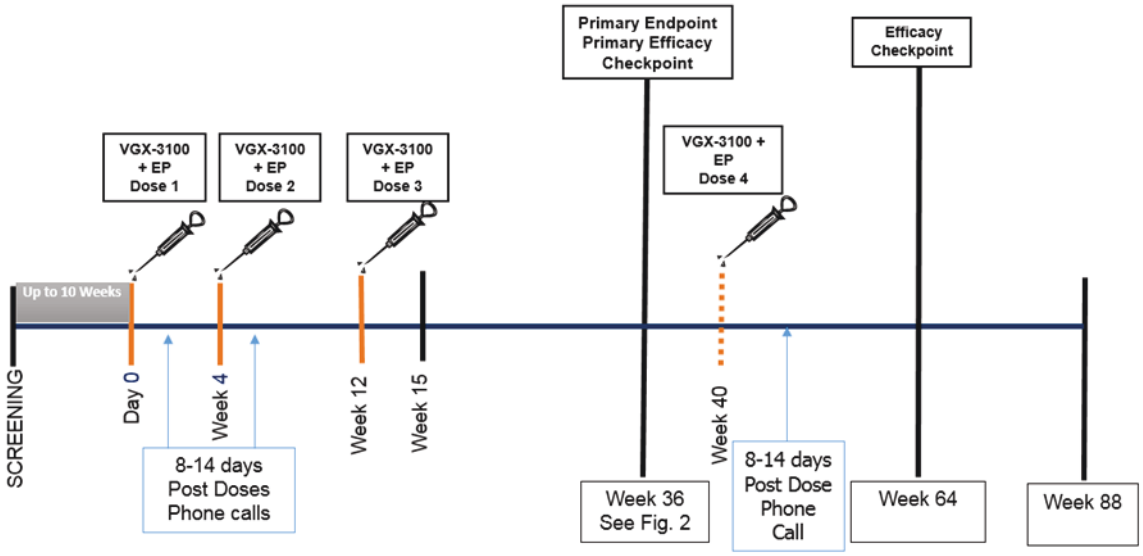
Study Design:

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or HPV-18.

Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40.

All subjects are scheduled to be followed to Week 88.

Figure 1: HPV-203 Study Visit Schedule



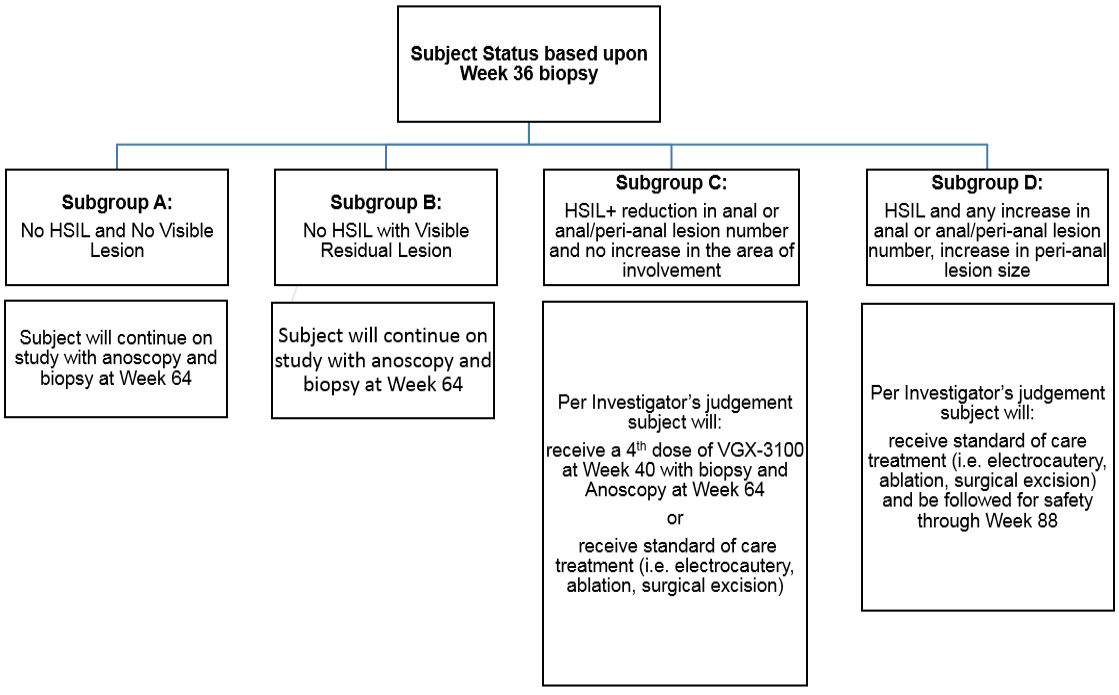
Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Subjects must also have intra-anal and/or peri-anal lesion(s) tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

Visualization of the lesion and digital anal rectal examination (DARE) alone are insufficient evidence to confirm disease regression. Disease regression will be primarily based on histopathologic assessment at Week 36 and additionally assessed at Week 64. Subjects will be monitored during the course of the study by DARE and HRA. Intra-anal lesion(s) will be assessed at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 using HRA. For all peri-anal lesion(s), standardized high resolution digital imaging will be used to assess the percent reduction in the cumulative surface area using pre-biopsy photographic imaging at Weeks 36, 64, and 88 compared to the post-biopsy photographic imaging of the previous biopsy visit.

The decision process following the results of the Week 36 biopsy are described below in ***Figure 2*** and are as follows: At Week 36, the subject will undergo repeat intra-anal and/or peri-anal punch biopsies of all HSIL lesions confirmed by the PAC at Screening of adequate size (≥ 4 mm). (See 1 for Minimally Required Biopsy Procedures). If after evaluation of the biopsy tissue(s) by the PAC there is no evidence of HSIL (defined by Subgroups A or B), the subject will continue to Week 64 for HRA and undergo biopsies of the same areas (HSIL lesions) as the baseline biopsies.

Figure 2: Decision process at Week 40



Pre-biopsy High Resolution Anoscopy Finding	Minimally required procedure
No lesion	Punch biopsy and photography; biopsy should be collected from within the approximate original boundaries of the study entry HSIL as proximal as possible to the original biopsy site which was previously determined to be HSIL by the PAC.
Single lesion (which was also present at baseline)	Punch biopsy and photography; biopsy should be collected within the boundaries of the original lesion and from the area most suspicious for advanced disease within the lesion by clinical exam.
Multiple lesions	Punch biopsies and photography; biopsy should be collected from the same lesions diagnosed as HSIL from study entry and from the area most suspicious for advanced disease within the lesion by clinical exam.

If HSIL is diagnosed in any Week 36 biopsy, but there is a reduction in the number of intra-anal and/or peri-anal lesion(s), reduction in peri-anal lesion(s) size or no change in peri-anal lesion(s) size from baseline (defined by Subgroup C), the Investigator has the option to administer a 4th dose of VGX-3100 at Week 40, and the subject will continue on the study to have HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may instead choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of standard of care.

In the event of worsening anal or anal/peri-anal HSIL at any time during the trial (defined as any increase in lesion(s) area from baseline or worsening of anal or anal/peri-anal HSIL to cancer), the subject may receive standard of care treatment (i.e. electrocautery, ablation, surgical excision) per the Investigator's judgment but will continue on the study through Week 88 with HRA, but without further biopsy unless it is part of the standard of care.

If there is histologic progression to carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment but will continue through Week 88 with HRA, but without further biopsy unless it is part of the standard of care. The event will be reported as an SAE per Section 7.3. If wide excision is required, the sample(s) obtained will be sent to the PAC for evaluation.

Efficacy Assessment:

Screening biopsies will be collected from all intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm). Visible lesion(s) observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and/or HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal tissue, utilizing HRA with biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Tissue samples will be analyzed for evidence of histopathologic regression. Clearance of HPV-16 and/or HPV-18 will be determined by type specific HPV PCR on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be collected at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types. Similarly, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) rinse samples will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy.

Immunogenicity Assessment: Humoral and cell mediated immune responses to VGX-3100 may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, 64, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of elevated immune responses at Week 36 as compared to baseline (Screening).

Virologic Assessment: Intra-anal and/or peri-anal swabs will be obtained to characterize HPV infection at Screening, Day 0, and Weeks 4, 15, 28, 36, 64 and 88 by PCR™. Likewise, PCR-based assessment of histological samples will occur at Screening and Weeks 36 and 64.

For testing of non-anal sites, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) samples (all subjects) will be obtained to characterize HPV infection at Day 0, and at Weeks 4,15, 28, 36, 64 and 88.

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

HLA haplotyping: A PBMC sample from any sample collected during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Safety Assessment: Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the Participant Diary Card (PCD).
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed to Week 88.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. Refer to Section 3.8 for stopping rule criteria.

Definition of Responder and Non-Responder for Primary Endpoint:

Responder and non-responder definitions (**Table 2**) take into account both histopathologic regression of anal or anal/peri-anal HSIL and virologic (HPV-16/18) clearance as measured by intra-anal and/or peri-anal tissue since HPV persistence is an important factor in the clinical progression of HSIL. Any case of histologically confirmed progression from HPV-16/18 positive anal or anal/peri-anal HSIL to carcinoma is considered a non-responder.

Table 2: Definition of Responder and Non-Responder for Primary Endpoint

Responder	Non-Responder
No histologic evidence of anal or anal/peri-anal HSIL AND Negative PCR for HPV-16 or HPV-18 in anal lesion tissue AND No non-study treatment of curative intent of intra-anal and/or peri-anal lesions	Histologic evidence of anal or anal/peri-anal HSIL, anal Adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma OR PCR positive for HPV-16 or HPV-18 in anal lesion tissue OR Any non-study treatment of curative intent of intra-anal and/or peri-anal lesions

Study Population:
Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2 within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16 and/or HPV-18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue specimens/slides provided to the Study Pathology Adjudication Committee (PAC) for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    a. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    a. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40mIU/mL;
    b. Surgically sterile due to absence of ovaries or due to bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    c. Subject agreement to avoid pregnancy for one month after last dose (Week 12 or Week 40);
    d. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of investigational product (Week 12 or Week 40). The following are acceptable methods:
        i. Hormonal contraception: either combined progestin-alone including oral contraceptive, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g. deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;
9. Men who would father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

Exclusion:

1. Untreated micro invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care for VAIN;
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care for VIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care for CIN;
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care for PIN;
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have completed and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator;
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    c. Long-term use (≥7 days) or oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, otic, nasal, topical, 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. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks of any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
17. 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 the study results (e.g. chronic renal failure, angina, myocardial ischemia or infarctation, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of Day 0;
20. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
21. 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;
22. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent form (participating in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrillator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or evaluation of any study product;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military personnel;
    d. Study-related staff or family members of study-related staff

TRIAL SCHEDULE OF EVENTS

Table 3: Schedule of Events

Study Action	Screen (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Informed consent	X												
Medical History/Demographics	X												
Medications (prior/concomitant)	X	X		X		X	X	X	X	X		X	X
Socio-behavioral assessment	X								X			X[o]	X
Inclusion/Exclusion criteria[1]	X	X											
Physical exam (PE)/assessment [a]	X	X		X		X	X	X	X	X		X	X
Vital signs	X[b]	X		X		X	X	X	X	X		X	X
Screening safety (12 lead ECG, laboratories) [c]	X												
Pregnancy Testing [d]	X	X		X		X	X	X	X	X		X	X
HIV Ab by ELISA	X								X				
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]			X[e]	X[e]
HLA testing [g]	X												
Oropharyngeal (OP) rinse		X		X			X	X	X			X	X
Vaginal, cervical, and penile swab		X		X			X	X	X			X	X
Intra-anal and/or peri-anal swab	X	X		X			X	X	X			X	X
Digital Anal Rectal Examination DARE [h]	X	X		X			X	X	X			X	X
High Resolution Anoscopy (HRA) [i]	X	X		X			X	X	X			X	X
Lesion photography [j]	X	X		X			X	X	X			X	X
Biopsy [k]	X								X			X	
Inject VGX-3100 +EP[l]		X		X		X				X[l]			
Post treatment reaction assessment		X		X		X				X			
Distribute Participant Diary Card (PDC)		X		X		X				X			
Review PDC [m]			X		X		X				X	X	
Patient Reported Outcomes (PROs) (SF-36v2™) (EQ-5D-5L) [n]		X[p]	X	X	X	X	X		X	X	X[q]	X	X

[1] Subject eligibility will be reconfirmed at every visit.

[a] Full Physical exam (PE) mandatory at Screening and study discharge (Week 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE.
[b] Screening vital signs must include a measured height and weight and calculated body mass index (BMI) (Bodyweight in kilograms divided by height in meters squared). Weight will be collected at all dosing visits.
[c] Screening 12-lead Electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatine (Cr), glucose, alanine aminotransferase (ALT), and Creatine Phosphokinase (CPK) performed within 30 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required for female subjects at Screening, prior to each study treatment, high-resolution anoscopy (HRA), and biopsy/surgical excision; the pregnancy test at Week 40 would only be needed for subjects who receive an additional dose.
[e] At least 42.5 mL (5 x 8.5 mL yellow (ACD) tubes) whole blood and 4 mL serum per time point. At least 68 mL whole blood and 8 mL serum should be collected prior to first dose.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 36.
[g] Human Leukocyte Antigen (HLA) testing will be performed once from an existing Peripheral Blood Mononuclear Cells (PBMC) sample.
[h] Digital Anal Rectal Examinations (DARE) are to be performed once cytology has been collected and prior to HRA.
[i] An additional visit may be scheduled to perform HRA if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening) and Weeks 36 and 64 for Subgroup C unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the Pathology Adjudication Committee (PAC) for review.
[j] Photography of intra-anal and/or peri-anal lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. Photographs of intra-anal lesion(s) will be for documentation purposes only. Photographs of peri-anal lesion(s) will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging at Weeks 36, 64, and 88 compared to the post-biopsy photographic image of the previous biopsy visit.
[k] Tissue specimen and slides from all excised tissue lesion(s) that led to eligibility at study entry must be reviewed by the PAC and residual tissue from entry and Weeks 36 and 64 specimen(s) (paraffin blocks or unstained slides) should be sent to the central laboratory for immune analysis and Human Papillomavirus (HPV) testing.
[l] Potential dosing at Week 40 is applicable for partial responders only.
[m] A phone call will be used to review the Participant Diary Card (PDC) with subject within 8-14 days following doses 1 and 2. The patient will be expected to bring the PDC to the next visit for review. Subjects who receive an additional 4th dose will have a phone call 8-14 days post dose 4 where the PDC will be reviewed.
[n] Patient-reported outcome (PRO) measures (SF-36v2™ and the EQ-5D-5L), plus two additional "global" questions will be assessed as described in Section 6.13.
[o] This socio-behavioral assessment will only apply to those subjects in Subgroup C who receive a 4th dose of investigational product.

[p] PROs must be administered prior to first dose of study drug.
[q] PROs will only be for subjects who received a 4th dose of study drug.

1.0 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. Human Papillomavirus 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). In the United States (US), approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type (HR-HPV) and thus can cause cancer [2]. In U.S. adults through age 59 years, about 25% of men and 20% of women have genital HR-HPV infection [3]. Human Papillomavirus causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV Deoxyribonucleic Acid (DNA) was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (OP), 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS) [4]. An average of over 30,000 cases per year of HPV-attributable cancer were diagnosed during the period 2008 through 2012 in the U.S. [5]. Human Papillomavirus-16 and HPV-18 are the most significant among high-risk types since they are responsible for most HPV-caused cancers [4].

With regard to anal cancer, about 95% of cases are caused by HPV, and most of those cases are caused by HPV-16 [6, 7]; with some by HPV-18 and perhaps other HPV genotypes [2]. An estimated 8,200 new cases of anal cancer in the US are diagnosed each year (for year 2017), with an estimated 1,100 deaths annually due to this cancer [8]. In Canada, the latest available data is for year 2013, during which 580 new cases of anal cancer were diagnosed and 144 persons died due to anal cancer [9].

The precursor lesion to HPV-associated anal cancer historically was known as anal high-grade dysplasia or intraepithelial neoplasia. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term HSIL to encompass high grade dysplasia [10]. Among HPV-associated anal HSIL cases in the US, about 55% to 80% are associated with HPV-16/18, and worldwide about 80% of cases are associated with HPV-16/18 [7, 11, 12].

Left untreated, anal HSIL may progress to cancer. Spontaneous regression of these lesions may occur, but the available data indicate that such regression is in the minority of cases. For example, published results of a small observational study of anal HSIL in men who have sex with men (MSM) in Australia found spontaneous regression occurred in 29% of those HIV-negative after more than one year of follow-up time, with an even lower regression rate in those who were HIV-positive. That study also found that the majority (71%) of patients who regressed only did so to anal low-grade SIL (Low grade squamous intraepithelial lesion [LSIL]), with the remainder to normal tissue [13]. In an ongoing larger observational study of gay and bisexual men – the Study of the Prevention of Anal Cancer (SPANC) [14] -- also comprised of patients HIV-negative and HIV-positive (though with medically well-controlled CD4 cell counts), preliminary published data show that 55% of patients with anal HSIL, regardless of HIV status, had their HSIL persist to at least 12 months and HPV-16 was significantly associated with persistence as compared to other HPV genotypes (Relative Risk of 1.5) [15].

Spontaneous regression data from that study are not yet published, but preliminary data show spontaneous regression of only about 20% by one year of follow-up. Further, many of those patients who regressed later recurred to HSIL, suggesting that HSIL in some cases may be merely regressing to a level below the detection limit but is still present [16]. Other published data from a sub-study of that larger study indicate that HPV-16 E6-specific T-cell responses may be associated with recent anal HSIL regression (Pexact = 0.065) [17]. That finding provides further plausibility, in addition to other data summarized later in this protocol, that VGX-3100 plus electroporation treatment could cause anal HSIL regression.

Anal HPV infection spontaneous clearance in non-immunocompromised adults can occur, but such data are generally unavailable for persons who have anal HSIL. Nevertheless, high-risk HPV (HR-HPV) clearance by one year ranges from 56% to 78%, varying by gender and sexual preference etc., as found in large, prospective studies [18-20] with some wider variation in clearance rates for HPV-16 and HPV-18 specifically in those studies.

Collectively, the aforementioned anal HSIL regression and HPV clearance data comprise in part the historical control data that the results of the present trial will be compared to.

1.1.1 VGX-3100

VGX-3100 contains plasmids that target HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated Investigational Product (IP) designed as a non-surgical treatment of HPV-16/18-related anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, and PAIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was Water for Injection (WFI) with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This frozen formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100 was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This non-frozen formulation of VGX-3100 was administered to 117 subjects in a Phase 1 clinical trial, HPV-101 in which subjects were randomized 1:1 to receive the non-frozen or frozen formulation of VGX-3100. In study HPV-101, healthy adults received three 6 mg IM doses of VGX-3100 in the frozen or non-frozen formulations followed by EP with the CELLECTRA™ 5Pdevice. The non-frozen formulation was found 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 enzyme-linked immunospot (ELIspot) assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (frozen formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16/18 [1]. The Phase 2b study, HPV-003, enrolled 169 subjects with high grade cervical dysplasia from seven countries and one US Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, US and Puerto Rico). Subjects were randomized in a 3:1 ratio to treatment with VGX-3100 or placebo, respectively. All

subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or Loop Electrical Excision Procedure (LEEP) of the cervix at Week 36 to assess efficacy defined as regression of high grade Cervical Intraepithelial Neoplasia (CIN) by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to Grade 1 Cervical Intraepithelial Neoplasia (CIN1) or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol (PP) and modified Intent to Treat (mITT) analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.2 ELECTROPORATION

CELLECTRA® 2000 & CELLECTRA™ 5PSP are both electroporation (EP) devices developed by INOVIO. Electroporation with CELLECTRA™5PSP 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 [21, 22]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced immunogenicity by 10 to 100 fold [23, 24]. 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 [21]. 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) [22, 23].

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 U.S. 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-16/18 related 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.

Inovio Pharmaceuticals Inc. device experience demonstrates that delivery of its proprietary electroporation pulses into muscle immediately following injection of DNA plasmids (including VGX-3100) is well-tolerated in humans and no significant safety issues have been identified [1, 22, 24]. For further information concerning the CELLECTRA™ 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.3 DOSE RATIONALE

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

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 (AEs) from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in HPV-003, Phase 2b study. The results obtained in the phase 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 2 trial [1].

1.2 POTENTIAL BENEFITS

Currently accepted surgical treatments are associated with a high recurrence rate, >50%. The current surgical approaches also have risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the anus. This study has been designed to provide non-surgical treatment with an aim of regression of the anal or anal/peri-anal HSIL and thus avoiding the need for surgical excision, infrared coagulation, electrocautery and laser therapy. In the absence of complete resolution of intra-anal and/or peri-anal lesions, there would still be potential benefit from a partial response, which would reduce or minimize the need for excisional or ablative treatment modalities. The other potential benefit is that the response to VGX-3100 is systemic and may clear the underlying HPV infection, which is the root cause. Consequently, there is the potential to reduce the risk of recurrence of anal or anal/peri-anal HSIL.

1.3 POTENTIAL RISKS

Risks associated with VGX-3100 for the treatment of anal or anal/peri-anal HSIL are injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience with VGX-3100 with healthy volunteers and in women with cervical HSIL, 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 anal dysplasia and possible missed diagnosis of an occult early invasive cancer for the VGX-3100 non-responders, who do not spontaneously regress. Although professional guidelines typically advocate excisional therapy for adults with HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [10]. The risk of a missed diagnosis of an occult early invasive cancer exists for all current treatment modalities including surgical and ablative therapies. To mitigate these potential risks the study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult

early invasive cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent High-resolution anoscopy (HRA) and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced physicians, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

An independent Data and Safety Monitoring Board (DSMB) will also advise the Sponsor if it appears that the frequency of regression is unacceptably low. These measures should minimize the risk of progression of the HSIL and the risk of harboring an undiagnosed occult early invasive cancer.

In the HPV-003 study of women with cervical HSIL, 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 and even lower than the 6.7% that has been reported under standard of care settings [18].

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

2.0 PURPOSE AND HYPOTHESIS

2.1 PURPOSE

To provide a treatment to potentially regress and clear HPV-16/18 related anal or anal/peri-anal HSIL in individuals that are seronegative for HIV-1/2.

2.2 HYPOTHESIS

VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal high-grade squamous intraepithelial lesions, HSIL, (AIN2, AIN3, PAIN2, PAIN3) associated with HPV-16/18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.

3.0 TRIAL DESIGN AND ENDPOINTS

HPV -203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or 18. Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40. All subjects are scheduled to be followed to Week 88.

To be eligible for the study, subjects must consent to participate and agree to the collection of anal lesion tissue samples for anal cytology and genotyping, a Digital Anal Rectal Examination (DARE), blood samples for immunologic and Human Leukocyte

Antigen (HLA) assessments, HRA and HRA guided biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4 mm) will be biopsied at Screening.

Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Subjects must also have intra-anal and/or peri-anal lesion tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

3.1 PRIMARY OBJECTIVE(S)

Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16/18

3.2 PRIMARY ENDPOINT(S)

Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL on histology (i.e., collected via biopsy or excisional treatment) and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue

3.3 SECONDARY OBJECTIVE(S)

- Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by testing from lesion tissue
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by intra-anal tissue swab testing
- Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in the size of peri-anal lesion(s), if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36
- Determine the humoral and cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline

3.4 ASSOCIATED SECONDARY ENDPOINT(S)

- Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC)
- **All** AEs including Serious Adverse Events (SAES), unanticipated (serious) adverse device effect (UADE), and other unexpected AEs for the duration of the study (through the Week 88 visit)
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
- Proportion of subjects with **no evidence** of anal or anal/peri-anal LSIL or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, and PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36
- Proportion of subjects with **no progression** of anal or anal/peri-anal HSIL to carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
- Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s) and the size of peri-anal lesion(s) if present, as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging at Weeks 36, 64, and 88 compared to the post-biopsy photographic imaging of the previous biopsy visit
- Levels of serum anti-HPV-16 and anti-HPV-18 antibody (Ab) concentrations at baseline and the Weeks 15, 36, 64, 88 visits
- Interferon- γ ELISpot response magnitudes at baseline, and the Weeks 15, 36, 64, and 88 visits
- Flow Cytometry response magnitudes at baseline and Week 15 visits

3.5 EXPLORATORY OBJECTIVE(S)

- Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16/18
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16/18
- Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples
- Describe the **clearance** of HPV-16/18 infection from non-anal anatomic locations

- Evaluate the effect of HLA type on **efficacy**
- Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression
- Describe PRO for subjects treated with VGX-3100

3.6 ASSOCIATED EXPLORATORY ENDPOINT(S)

- Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
- Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
- Assessment of immunologic markers (e.g. CD8+ and FoxP3+ infiltrating cells). Additional assessments may include Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows.
- Proportion of subjects who have **cleared** HPV-16/18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
- HLA (per-locus and per-allele basis) in conjunction with **histologic regression** of anal or anal/peri-anal HSIL at Week 36 visit
- HRA, cytology, and HPV test results and miRNA profile (baseline and at Weeks 15, 28, and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit
- Patient reported outcome endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose.

3.7 EFFICACY ASSESSMENT

Screening biopsies will be collected from all intra-anal and/or peri-anal lesions of adequate size (≥4mm). Visible lesions observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal and/or peri-anal tissue obtained from biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from

all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Tissue will be analyzed for evidence of histopathologic regression. Clearance of HPV-16/18 will be determined by type specific HPV polymerase chain reaction (PCR) on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0 (prior to dosing) and Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types. Similarly, vaginal, cervical (female subjects), penile (male subjects) and OP rinse samples (all subjects) will be obtained at Day 0 (prior to dosing), and at Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of the standard of care. All tissue samples obtained from biopsies or removed per standard of care will be sent to the PAC for review.

3.8 SAFETY ASSESSMENT

Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the PDC.
2) All AEs including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed for 88 weeks.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. The following stopping rules will be applied:

- If at any time during the study one-third (1/3) or more of the subjects experience an Adverse Event of Special Interest (AESI), further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AEs) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 AEs, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- The Sponsor or Designee will notify all Investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

3.9 IMMUNOGENICITY ASSESSMENT

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

4.0 TRIAL POPULATION

4.1 INCLUSION CRITERIA

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2 within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16/18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue specimen/slides provided to the Study PAC for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    i. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    i. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with follicle-stimulating hormone (FSH) level >40mIU/mL;
    ii. Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    iii. Subject agreement to avoid pregnancy one month after last dose of IP (Week 12 or Week 40);

iv. Women of Childbearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of IP (Week 12 or Week 40). The following are acceptable methods:

1. 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);
2. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
3. Intrauterine device or intrauterine system;
4. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;

9. Men who could father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

4.2 EXCLUSION CRITERIA

1. Untreated micro invasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care for VAIN;
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care for VIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care for CIN;
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care for PIN;
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;

10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 30 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator;
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    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, nasal, topical, 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 Tumor Necrosis Factor (TNF)-α inhibitors (e.g. infliximab, adalmumab or etanercept);
    e. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks of any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treated as deemed by the Investigator;
17. 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);
18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of a study dose;
20. History of seizures unless seizure free to 5 years with the use of one or fewer antiepileptic agents;
21. 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;

22. Resting heart rate <50 beats per minute (bpm) (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing the ICF (participation in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrilator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. 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;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntary incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military service personnel;
    d. Study-related staff or family members of study-related staff

4.3 DISCONTINUATION/WITHDRAWAL OF TRIAL SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION FROM THE STUDY

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from further treatment with VGX-3100. Subjects will not receive further doses of VGX-3100 followed by EP but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests a Grade 3 toxicity attributable to VGX-3100/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM STUDY

Subjects who become ineligible to continue on the study based on no longer meeting the inclusion criteria should be discontinued from study treatment and managed per routine standard of care but should continue on the study without further biopsy.

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 anal or anal/peri-anal HSIL, and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls to the subject should be made and if that fails, then a certified letter is sent to the subject's last known mailing address) so that they can be considered withdrawn from the study for disposition purposes. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will the subject be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

If a subject elects to discontinue treatment/EP they should be encouraged to stay in the study and complete all follow-up visits and procedures and have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events (Table 3). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 88). A subject will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs and/or SAES present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 – Safety Parameters.

4.3.4 REASONS FOR DISCONTINUATION/WITHDRAWAL

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

- 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 AEs regardless of relation to study drug.
- Death of a subject, (including manner of death if known)
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the eCRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a maternal obstetrical or medical need to withdraw subject.

Investigator must consult the Medical Monitor before withdrawing a subject from participation in the study.

- Protocol Deviation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g. treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including 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 who receive study treatment and discontinue prior to Week 36, primary endpoint procedures, then supplementation of study subjects will be considered.

5.0 TRIAL TREATMENT

5.1 INVESTIGATIONAL BIOLOGIC PRODUCT

The IP to be used in this trial is described in Table 4. The IP will be presented in a clear glass cartridge and injected intramuscularly.

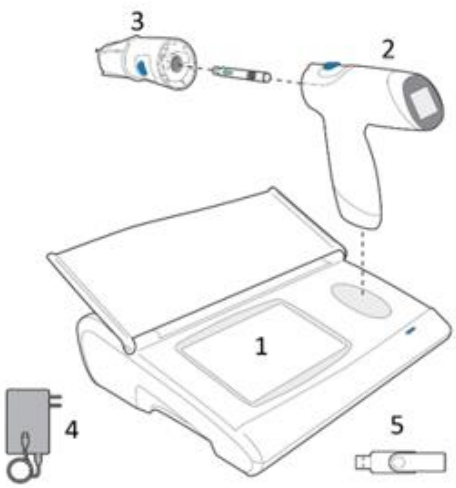
Table 4: Investigational Biologic Product

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

5.2 CELLECTRA™ 5PSP DEVICE DESCRIPTION:

VGX-3100 will be delivered using the CELLECTRA™5PSP device. The device consists of five (5) main components (see Figure 3).

Figure 3: CELLECTRA™5PSP Base Station with Handset



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

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

3) CELLECTRA™ 5PSP Sterile Single Use Array which consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

4) USB International Power Supply

5) Flash Drive

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset.

Handset

The handset facilitates delivery of the needles for injection and electroporation into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit and is compliant to International Ethics Committee (IEC) 62133 and UL 2054. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire.

Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 IM injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array

(indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The 5PSP Array features no software.

The base station and handset with the 5PSP Array are illustrated in

Figure 3.

5.3 TREATMENT REGIMEN

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-203 study will receive the same three 6 mg doses of VGX-3100 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 at Week 12. A fourth dose may be administered at Week 40.

The first study treatment will be given as soon as possible following confirmation of anal or anal/peri-anal 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.

5.4 PACKAGING AND HANDLING

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, single-panel label with tear-off. The VGX-3100 label will include, at minimum, the following information in Table 5.

Table 5: Example of Packaging and Label Information

Cartridges (primary container)	**Pouches** (secondary packaging)
LABEL VGX-3100 Insert cap end Sponsor name IM administration Investigational Use Only	**LABEL BODY** Study ID VGX-3100 Single-use cartridge containing 1 mL IM administration via CELLECTRA™ 5PSP Store at 2-8°C, expiration date Caution Statement Sponsor name and address
	LABEL TEAR OFF Study ID VGX-3100 Patient ID: _____ Date: (DD-MMM-YYYY): _____ Must be used by (time): _____

See Figure 4 below for example of CELLECTRA™ 5PSP device component labels.

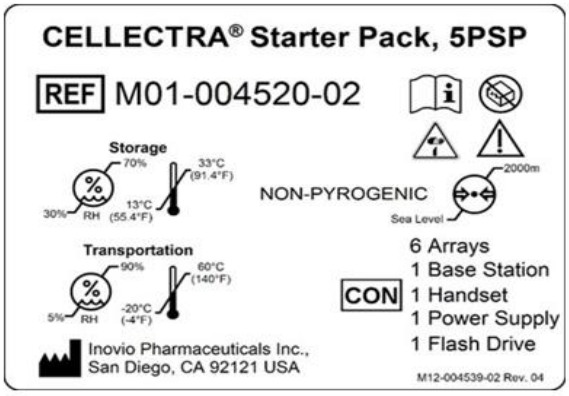
Figure 4: Examples of Device Labels (Base, Handset, Array, Outer Box)

Base Station Label

Handset Label

5PSP Array Label

Outer Box Packaging Label



5.5 HANDLING AND STORAGE OF IP AND DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual. The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and relative humidity ranges of 30-70%. The Sponsor should be notified of any deviations from this recommended storage condition.

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. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. The Sponsor should be notified of any deviations from this recommended storage condition. Inovio Pharmaceuticals Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. For the specific

temperature guidelines for storing, please refer to the CELLECTRA™ 5PSP User Manual.

5.6 PREPARATION AND DISPENSING

It is the responsibility of the Investigator to ensure that VGX-3100 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, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration.

The pouch must not be discarded until:

1. Administration is completed and
2. All pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator. If VGX-3100 is not used within this timeframe it must be discarded after reconciliation.

5.7 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of the 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. Refer to the User Manual for further instruction. 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.

5.8 DRUG AND DEVICE ACCOUNTABILITY

5.8.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of IP 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;
- Date and initials of person responsible for each IP inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;

- Amount destroyed at study site, if applicable

5.8.2 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The site is responsible for maintaining the device. The device must have full traceability from receipt of the products through the subject use, and the return of the device. The site must document acknowledgement of receipt and then notify INOVIO upon receipt of the device. This includes the content shipped and condition of the items upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP Base Station & Handset serial number, 5PSP 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.

5.9 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT AND CELLECTRA™ 5PSP DEVICE

5.9.1 RETURN OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at the site per the institutions policy or returned to INOVIO or its designee, if the site cannot destroy the unused IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site. Do not attempt to remove the cartridge from the array once it has been used.

It is the Investigator's responsibility to arrange for the 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 personal or designated Study Monitor.

If IP is returned to INOVIO, 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. The return of unused IP(s) should be arranged with the responsible INOVIO personnel and/or Clinical Monitor.

5.9.2 RETURN OF CELLECTRA™ 5PSP DEVICE

Upon completion or termination of the study, all investigational devices and unused components (Base, Station, Handset, and 5PSP Arrays) must be returned to INOVIO.

All device components returned to INOVIO 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.

If any component is to be 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, 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.

6.0 TRIAL 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 3).

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

Protocol waivers or exemptions will not be granted. 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 3) are essential and required for study conduct. Subject eligibility should be reconfirmed at every study visit.

6.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial subjects, explain the trial, and provide them with an ICF that describes the Screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial 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 trial 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.

6.2 BEFORE TREATMENT PROCEDURES

Subjects who consent to participate will have biopsy slides or paraffin-embedded tissue block(s) from a previous biopsy and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the 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), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with anal or anal/peri-anal HSIL, by a local pathologist, where the initial biopsy tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, an additional biopsy sample should be collected during Screening following the consent of the subject. The 10 week Screening window begins upon collection of the biopsy sample that will be evaluated by the PAC.

At Screening, subjects must have a diagnosis of histologic anal or anal/peri-anal HSIL confirmed by the PAC and intra-anal and/or peri-anal specimen test positive for HPV-16/18 by PCR to be eligible for participation in the study (provided the subject also

meets other eligibility criteria). Subjects whose intra-anal and/or peri-anal specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16/18.

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

6.2.1 SCREENING EVALUATIONS

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the safety laboratory collections/assessments, which must be performed within 30 days prior to Day 0. All Screening assessment values must be reviewed ***prior*** to study treatment. Some of these evaluations/actions will be performed again later in the trial (see later text and the Schedule of Events Table 3 for more detail).

- Signed ICF
- Medical history/demographics, including history of prior anal or anal/peri-anal HSIL
- Socio-Behavioral Assessment; including smoking history, exposure to second-hand smoke, alcohol intake history, recreational drug use and contraceptive use
- Prior concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Complete Physical Examination
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate), height, weight and body mass index (BMI) measurements
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (including complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatine (Cr), glucose, alanine aminotransferase [ALT], and creatine phosphokinase [CPK]) (to be performed within 30 days prior to Day 0)
- Urine pregnancy test
- Serology (HIV Ab) within 30 days prior to Day 0
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- Digital Anal Rectal Examination (DARE)
- High Resolution Anoscopy (HRA)
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (slides from all excised tissue must be reviewed by the PAC).
- Whole blood (at least 68 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile

6.3 DURING TREATMENT PROCEDURES BY VISIT

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

6.3.1 DAY 0

The following study evaluations will be performed at Day 0 (unless noted) prior to the first study treatment:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcome (SF-36v2™ and EQ-5D-5L) (may be performed at Day -1 or on Day 0, again provided it is done prior to the first study treatment)
- Study treatment administration

The following evaluations will be performed on Day 0 after study treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during the phone call:

- Review Day 0 of 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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.3 WEEK 4 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant mediation review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient report outcomes (SF-36v2™ and EQ-5D-5L)
- Collect PDC for dose 1
- Study treatment administration

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

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

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during the phone call:

- Review of PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.5 WEEK 12 (± 4 DAYS)

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

- Reconfirm subject eligibility

- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect and review PDC for dose 2
- Study treatment administration

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

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.6 WEEK 15 (± 1 WEEK)

The following study evaluations will be performed at Week 15:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.7 WEEK 28 (± 1 WEEK)

The following study evaluations will be performed at Week 28:

- Reconfirm subject eligibility

- Concomitant medical review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)

6.3.8 WEEK 36 (± 1 WEEK)

The following study evaluations will be performed at Week 36:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks or unstained slides)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.9 WEEK 40 (± 1 WEEK)

The following study evaluations will be performed at Week 40:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Study treatment administration
- Based on biopsy results collected at Week 36 and Investigator judgment, a 4th dose may be given at this visit

****Please remember to download EP data from CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

The following study evaluations will be performed at the Week 40 post treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Patient reported outcomes-only the two "global" questions for this visit

6.3.10 8-14 DAYS POST DOSE 4 PHONE CALL (FOR SUBJECTS WHO RECEIVED A 4TH DOSE)

The following information will be evaluated during the phone call:

- Review PDC for dose 4 (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)

6.3.11 WEEK 64 (± 2 WEEKS)

The following study evaluations will be performed at Week 64:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment (only for subjects who received a 4th dose at Week 40)
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swab

- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks or unstained slides) for subjects who received a 4th dose at Week 40
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.12 WEEK 88 (± 2 WEEKS)

The following study evaluations will be performed at Week 88:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Urine pregnancy test
- Vital signs
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.4 TRIAL PROCEDURES

6.5 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all trial-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., ANUS01001). 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.

6.6 DEMOGRAPHICS

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

- Age
- Gender
- Race/ethnicity
- Dominant hand/arm

6.7 SAFETY EVALUATIONS

6.7.1 PHYSICAL EXAM

A full Physical exam (PE) will be conducted during Screening and study discharge (Week 88). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems, and a DARE.

A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

6.7.2 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 prior to measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.7.3 HEIGHT AND WEIGHT

Weight and height will be collected at all dosing visits in order to calculate the BMI.

6.7.4 MEDICAL HISTORY

Medical history, including history of prior anal or anal/peri-anal dysplasia and gynecologic history will be obtained at Screening. For females, previous history of treatment for VIN, CIN and/or VAIN will be collected. All relevant past and present conditions, as well as prior surgical procedures at least 6 months prior to enrollment will be recorded for the main body systems.

6.7.5 SOCIO-BEHAVIORAL ASSESSMENTS

Socio-Behavioral Assessment, including self-reporting of the following: smoking history, history of exposure to second-hand smoke, alcohol intake history, recreational drug use history, history of contraceptive use and type of contraceptive if known, reproductive history, sexual preference and sexual practices history, and pregnancy history will be obtained at Screening.

At Weeks 36, 64, and 88, a socio-behavioral assessment will be performed again to document any changes from Screening and/or other time periods.

6.7.6 LABORATORY EVALUATIONS

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

Complete Blood Count:

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

Serum Chemistry:

- Glucose
- Blood urea nitrogen
- Creatine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase

6.7.7 PREGNANCY TESTING

For women of reproductive potential, a negative spot urine pregnancy test is required at Screening, and prior to each study treatment, HRA, DARE and surgical excision or biopsy.

6.7.8 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.

6.7.9 PARTICIPANT DIARY CARD (PDC)

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 11:59pm)
- 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 days post dose phone calls and at the next in-person visits.

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 criteria for a Grade 1 or higher AEs should be documented as an AE 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.

6.8 INJECTION AND ELECTROPORATION (EP)

Subjects will receive at least three doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by IM injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 5PSP. A fourth dose is optional for those assessed to be partial responders at the Week 36 efficacy assessment. Study treatment plus EP must not be given within 2 cm of a tattoo, keloid or hypertrophic scar, or if there is implanted metal within the same limb. EP may not be performed in the same arm adjacent to an implantable medical device (e.g., cardiac pacemaker, defibrillator or retained leads following device removal). The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, and at Week 40 (for Subgroup C only). Please refer to the Investigator's Brochure for further information.

6.9 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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, and Weeks 4 and/or Week 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.

6.10 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 into the study as listed in the Schedule of Events (Table 3).

6.11 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

The injection site will be assessed by study personnel prior to and between 30-45 minutes after each study treatment. Subjects will be advised to record local and systemic AEs for 7 days after each study treatment on a PDC which will be reviewed with study personnel 8 – 14 days after doses 1 and 2, Week 15, and 8-14 days after dose 4 (if applicable).

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any AEs, 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 AEs will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's Case Report Form (CRF).

6.12 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 6.

Table 6: 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 "Food and Drug Administration (FDA) Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" *In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

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

6.13 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, PRO instruments will be administered. The following PRO questionnaires will be used:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [25]. SF-36v2™ will be administered at the following time points:
  - Day 0 (*before* the first study treatment)
  - 8-14 days post dose 1
  - Week 4
  - 8-14 days post dose 2
  - Weeks 12, 15, 36, 40
  - 8-14 days post dose 4
  - Weeks 64, 88
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [26, 27] and will be administered as described below:
  - Day 0 (*before* the first study treatment)
  - 8-14 days post dose 1
  - Week 4
  - 8-14 days post dose 2
  - Weeks 12, 15, 36, 40
  - 8-14 days post dose 4
  - Weeks 64, 88

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

- **Additional Global PRO Questions-** regarding quality of life after surgery or biopsy. These two questions will be administered at Week 40 only.

6.14 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (Screening and Day 0 prior to dosing) and at Weeks 15, 36, 64 and 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding enzyme-linked immunosorbent assay (ELISA) may be performed to measure the anti–HPV-16/18 Ab response induced by VGX-3100.

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

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 and Weeks 15 and 36. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

6.15 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks may be collected for immune analysis. Assessment of markers may include, but are not limited to, CD8+ and FoxP3+ infiltrating cells as well as Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.16 HUMAN LEUKOCYTE ANTIGEN TYPING

Human Leukocyte Antigen testing will be performed on PBMC from a single blood sample collected for immunogenicity analysis if available.

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

6.17 ANAL AND/OR PERI-ANAL HPV TESTING

All intra-anal and/or peri-anal lesions of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL sites(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression.

The subject will be requested to abstain from sexual activity and refrain from the use of douching to eliminate potential interference with the results of HPV testing.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 using ThinPrep™. An HPV PCR test will be performed on the ThinPrep™ specimens at Screening, and Weeks 36 and 64 when applicable. At each of these visits, a recent history will be collected via self-report.

6.18 HPV TESTING FROM OTHER ANATOMICAL SITE (NON-ANAL)

Vaginal, cervical (female subjects), penile (male subjects), and OP rinse samples (all subjects) will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess virologic clearance at non-anal sites. All samples will be read in a central laboratory.

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

6.19 ANAL PHOTOGRAPHS AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of anal or anal/peri-anal HSIL confirmed by the PAC at Screening. Subjects will undergo HRA at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 to identify all intra-anal lesion(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression.

Photography of all intra-anal and/or peri-anal lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. Photographs of intra-anal lesion(s) will be for documentation purposes only. For all peri-anal lesion(s), digital photographs will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging at Weeks 36, 64, and 88 compared to the post-biopsy photographic image of the previous biopsy visit.

If the intra-anal and/or peri-anal tissue sample(s) result suggests progression to cancer, the Investigator may schedule an ad hoc visit to perform HRA and possible biopsy if clinically indicated.

6.20 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 will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and the Investigator's judgment based on the results of the histological diagnosis from the unscheduled biopsy. All biopsy samples/excised tissue (including standard of care) will be sent to the central pathology lab for review by the PAC.

6.21 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 the 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, nasal, topical, 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.

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.

6.22 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, including illicit drugs, taken to the Investigator and/or other study personnel. To remain in the study, illicit drugs should not be taken.

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

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

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

As a requirement for inclusion in the HPV-203 study, Investigators will only be chosen if they are experienced in the management of anal cancer, and are experienced in performing HRA.

HPV-203 Investigators are instructed to perform additional, ad hoc HRA exams and biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analyses. These additional measures should minimize the risk of progression of anal or anal/peri-anal HSIL and the risk of harboring an undiagnosed occult early invasive anal or anal/peri-anal cancer. The frequency of close monitoring by experienced Investigators should minimize the risk of cancer progression during the study and the additional measures are beyond what is expected in standard of care.

7.2 ADVERSE EVENTS (AEs)

An 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 AEs 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 IP. Adverse Events 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.

Adverse Events 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 increased 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 demise, still birth, congenital anomaly of fetus/newborn);
- AEs that occur from the study Screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE;
- Conditions that lead to a medical or surgical procedure.

Adverse Events do not include the following:

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

7.3 SERIOUS ADVERSE EVENTS

A SAE is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation).

However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an Emergency room (ER) or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, or 3) the development of drug dependency or drug abuse.

Classification of Serious Adverse Events:

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

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.15.

7.4 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose; for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the AEs. An AE 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 ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory

authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of serious expected AEs, 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

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 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 and clinical AEs or SAEs with respect to the following levels of severity as per CTCAE v 4.03 for applicable patient populations:

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

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

7.7 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable causal relationship to the administration to either or both IP and/or the CELLECTRA™ 5PSP device. The Investigator will assess causal relationship of the AE separately to each of the investigational drugs and also the investigational device. The reasonable causal relationship means that there are facts (evidence) or arguments to suggest a causal relationship. An AE may also be assessed as not related to either or both IP and/or investigational device. Because the Investigator is knowledgeable about the subject

(e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs 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 AE 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 VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation or deemed clinically significant by the Investigator must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, and 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 Sections 7.2 and 7.3. 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 is assessed as detailed in Section 7.6.

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT).

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines not only the severity of the event but also whether the abnormality in question is "clinically significant (CS)" or "NCS." CTCAE v. 4.03 grading criteria can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.9 POST-TRIAL 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 probably or possibly related to the study treatment, he/she should promptly document and report the event to the Sponsor.

7.10 PROCEDURES FOR DOCUMENTING PREGNANCY DURING THE TRIAL

Subjects who are pregnant or expect to become pregnant during the course of the study will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further treatments with the IP. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax or email, as described in Section 7.15. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further 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 Screening procedure through the follow up visits must be reported. The Investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the Sponsor.

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up

period. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.11 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 88.

The sources of AEs cover:

1. The subject's response to questions about his/her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF.

Any SAE occurring during the course of the study must be reported to the Sponsor within 24 hours of awareness.

7.12 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 AEs classified by system organ class (SOC), preferred term, severity, and relationship to study treatment;
- Changes in safety laboratory parameters (e.g., hematology and serum chemistry);
- 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.

7.12.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with Cellectra™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

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

Sites will inform the Sponsor via method described in Section 7.15 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.13 ADVERSE EVENT REPORTING

To assure the safety of the participants, information about all AEs (see Section 7.2), whether volunteered by the subject, discovered by the 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.

7.14 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited AEs will be collected throughout the study and recorded in the Electronic Data Capture (EDC) system. The Study Report will analyze and summarize all AEs throughout the study. Emphasis will be placed on the following:

1. Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately
2. Unsolicited AEs will be collected and summarized for the entire study period

7.15 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS AND AESIS

The reporting period for SAEs (without regard to causality or relationship) and AESIs is comprised of the period following the signing of the ICF through Week 88. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator will complete the SAE/AESI Report form and report the event to the Sponsor within 24 hours of becoming aware of the event. The Investigator may also directly report this event to the EC according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.5 (UADE) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant 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.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the Investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the

event related to prior Study Treatment, the Investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION

MEDICAL MONITOR: [redacted], M.D., Ph. D.
EMAIL: [redacted]

SAE REPORTING INFORMATION

EMAIL: safety.inovio@apcerls.com
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is an attachment to an e-mail message, to the email address as indicated above. Any SAE supporting documents provided by facsimile (Fax) are to include a coversheet that identifies the reporter name and contact information of the study site.

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.

In addition to providing the SAE report to the Sponsor or designee within 24 hours of becoming aware of the event, the AE that is serious must be recorded in the AEs eCRF. The entry into the eCRF is required to be done as soon as possible.

The Investigator will supply the Sponsor and the IRB with more information as it becomes available and any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

When recording the SAE form, correct medical terminology/concepts are to be used and the use of abbreviations and colloquialisms are to be avoided.

Serious Adverse Events 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.

In the event of a pregnancy, the Investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

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 experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.4 and 7.16).

7.17 REPORTING OF CELLECTRA™5PSP DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported within 24 hours of becoming aware of the event per Sections 7.2 and 7.3.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form provided must be completed and emailed to the Sponsor at clinicalcomplaint@inovio.com.

Additional instructions on complaint reporting to be provided separately.

7.18 TRIAL DISCONTINUATION

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

Should the trial be terminated and/or the site closed for any reason, all investigational drugs & devices must be returned to INOVIO or its representative. The PI should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 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 or its representative.

This is a single-arm, multi-center, open-label clinical trial of VGX-3100 in subjects with a diagnosis of AIN2, AIN3, PAIN2, or PAIN3 associated with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of AIN/PAIN HSIL and viral clearance of HPV-16/18 based on tissue collected at Week 36. The primary hypothesis is that the treatment will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16/18 infection, complete regression, non-progression, and anatomic extent. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory efficacy analyses concern extended dosing with respect to regression, clearance, clearance among non-anal anatomic locations, and effect of HLA type on efficacy and association of miRNA profile, anoscopy, cytology, and virology with efficacy. Other exploratory analyses pertain to tissue immunological measures and PRO.

8.3 STATISTICAL HYPOTHESES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations are:

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.05 and the corresponding lower bound of the one-sided 95% CI exceeds 0.15.

For the analysis, the efficacy time frame is defined by any time starting from 14 days prior to the -specified visit week.

8.5.2 SECONDARY ANALYSES

The secondary efficacy binary 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.

The anatomic extent endpoint will be analyzed by calculating the mean percent change in surface area and the mean percent change in number of lesions and associated 95% t-distribution based confidence intervals.

Post-baseline ELISA titers will be summarized with geometric mean and associated 95% CIs. Post-baseline increases in ELISPOT and Flow responses will be summarized with tobit-based means and 95% CIs. Valid samples for statistical analysis purposes will be those collected within 14 days of the specified visits. Baseline is defined as the last measurement prior to the first treatment administration.

8.5.3 SAFETY ANALYSES

All AEs will be summarized among the safety population by frequency. These frequencies will be presented overall and separately by dose, and will depict overall, by SOC 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 AE data will be based on events occurring within 28 days following any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days following any dose and regardless of when they occurred.

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

8.5.4 DISPOSITION

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

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables for the mITT population.

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

Prior medications are those that were used and stopped 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. Data for all prior medications will be summarized with percentages for the mITT population.

8.5.6 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 will not be adjusted for possible early stopping due to futility.

8.5.7 MULTIPLICITY

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

8.5.8 MISSING VALUES

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.

No other missing data will be imputed or replaced.

8.5.9 EXPLORATORY ANALYSES

The exploratory efficacy binary 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.

Other analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) HRA results, d) cytology results, and e) HPV results. Relationships will be examined with contingency tables and/or logistic regression models which model the primary endpoint versus these results as regressor variables.

The change in tissue immune response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.6 SAMPLE SIZE/POWER

A sample of 24 subjects provides ~80% power to declare superiority over historical control, assuming the true proportion of subjects who achieve the primary endpoint is 40% for the treatment arm versus 15% for the historical control, and that 90% are evaluable at Week 36 from 1st dose.

8.7 RANDOMIZATION AND BLINDING

This is an open-label trial, and therefore, site personnel, individual subjects and INOVIO or its representative trial personnel will be aware of the treatment allocations for this trial. Randomization does not apply.

9.0 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical trial 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

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., ICF, 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:

- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of trial-related information (refer to trial files) that include all correspondence with the IRB/EC.
- Notify the IRB/EC when the trial is completed (i.e. after the last visit of the final trial subject).
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.

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 OFFICE OF BIOTECHNOLOGY ACTIVITIES

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 [NIH] Office of Biotechnology Activities [OBA]) governing research that involves recombinant or synthetic nucleic acid.

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 trial, 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 (Section 6.1).

9.5.2 COMPLIANCE WITH IRB/EC REQUIREMENTS

This trial 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 trial 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.

9.5.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURE REGULATIONS (21CRF PART 11)

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

9.5.5 COMPLIANCE WITH PROTOCOL

Subjects will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviation (PD), should a deviation be discovered, Sponsor must be informed immediately. Any PD 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 prior review and documented approval/favorable opinion from the Sponsor and IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects. While every effort should be made to avoid PD, should a deviation be discovered, Sponsor must be informed immediately. Any PD impacting Subject safety must be reported to the Medical Monitor immediately.

10.0 DATA COLLECTION, MONITORING, AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial 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 trial Sponsor, the governing health

authorities or the FDA, if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

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

Information about trial subjects will be kept confidential and managed in accordance with the requirements of the HIPAA of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

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

11.0 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 trial.

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.

Case Report Form will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified with an SID.

It is the Investigator's responsibility to retain trial essential documents for at least two (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 two (2)

years have elapsed since the formal discontinuation of clinical development of the IP. 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.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY AND QUALITY MONITORING

An independent 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 there appears to be a regression with VGX-3100.However, no formal interim analysis will be performed.

12.2 PATHOLOGY ADJUDICATION COMMITTEE

All anal biopsies will be read by a central expert PAC to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion. If the two pathologists agree the reading will be considered the clinical disease status for the subject. If the readings of the first two pathologists are discordant, the third pathologist will review the discordant slide(s) independently and if there is agreement among any of the three readings, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the most severe diagnosis would be deemed the final diagnosis.

12.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:
    - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
    - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities continue to be acceptable.
- Compare the trial 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.

13.0 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 at least 60 days prior to submission for publication. The Sponsor will have 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) will 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 US Patent and Trademark Office and/or foreign patent office(s).

14.0 LIST OF ABBREVIATIONS

Ab	Antibody
ADR	Adverse Drug Reaction
AEs	Adverse events
AESI	Adverse Event of Special Interest
AIN	Anal Intraepithelial Neoplasia
AIS	Adenocarcinoma-in-situ
ALT	Alanine Aminotransferase
BMI	Body Mass Index
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIN	Cervical Intraepithelial Neoplasia
CIN1	Grade 1 Cervical Intraepithelial Neoplasia
CIOMS-I	Council for International Organizations of Medical Sciences
Cr	Creatine
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CPK	Creatine Phosphokinase
DARE	Digital Anal Rectal Examination
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
ELIspot	Enzyme-linked Immunospot Assay
EP	Electroporation with CELLECTRA™5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ER	Emergency Room
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
gbm	gay and bisexual men
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HRA	High-resolution Anoscopy
HR-HPV	High-risk HPV Type
HSIL	High Grade Squamous Intraepithelial Lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug

INOVIO	Inovio Pharmaceuticals, Inc.
IP	Investigational Product
IRB	Institutional Review Board
IRB/IEC	Institutional Review Board or Independent Ethics Committee
ISO	International Organization for Standardization
LAST	Lower Anogenital Squamous Terminology
LSIL	Low Grade Squamous Intraepithelial Lesion
miRNA	MicroRNA
mITT	Modified Intent to Treat
MSM	men who have sex with men
NCS	Not Clinically Significant
OBA	Office of Biotechnology Activities
OP	Ororpharyngeal
PAIN	Peri-anal Intraepithelial Neoplasia
PAM	Protocol Administrative Memo or Letter
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIN	Penile Intraepithelial Neoplasia
PP	Per Protocol
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PE	Physical Exam
PRO	Patient-reported Outcome
SAEs	Serious Adverse Events
SF-36v2™	36-Item Short Form Health Survey
SID	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPANC	Study of the Prevention of Anal Cancer
SSC	Saline Sodium Citrate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumor Necrosis Factor
UADE	Unanticipated (Serious) Adverse Device Effect
US	United States
VAIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
WFI	Water for Injection
WOCBP	Women of Childbearing Potential

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16.0 APPENDICES

HPV-203

A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal, High grade squamous intraepithelial lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 13683

Protocol Version: 1.1
Protocol Version Date: 08Nov2017

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.0 dated 15 September 2017 to Version 1.1 dated 08 November 2017. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Associated secondary endpoint #7 currently states: 'Percent reduction in the number of intra-anal and/or peri-anal lesion(s) as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging at Week 36, 64, and 88 compared to the post-biopsy photographic image of the previous biopsy visit. The new associated secondary endpoint #7 will read as follows and has been updated to reflect this throughout the protocol: Percent reduction in the number of intra-anal and/or peri-anal lesion(s) as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Weeks 36, 64, and 88 compared to baseline.
2. The definition of baseline photographic imaging has been provided and is defined as follows: photographs obtained pre-biopsy at Screening, or post biopsy at Screening (for subjects with historical biopsy tissue).
3. The definition of qualifying lesion(s) has been added and the definition is as follows: an intra-anal and/or peri-anal lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed anal or anal/peri-anal HSIL by the Pathology Adjudication Committee (PAC).
4. Exclusion criteria numbers 2, 3, 4, and 5: Subjects who are under the care of a health provider for their biopsy-proven VAIN, AIN, CIN, or PIN but may not be receiving treatment are eligible for this trial. There criteria were modified in consideration of subjects who are under medical surveillance by their healthcare provider.
5. Exclusion criteria #11: has extended the window for use of clinical laboratory results at Screening from 30 days to 45 days. This allows subjects to use safety lab results and ECG results within 45 days prior to Day 0 to determine eligibility.
6. Per Table 3 Schedule of Events for blood immunologic samples: Subjects will have 34 ml of whole blood and 4 ml of serum drawn per time point. At Screening and Day 0, a total of at least 68 ml of whole blood and 8 ml of serum will be collected. Additionally, the current protocol (15 Sep 2017) indicates that at Week

36, subjects will have at least 51 ml of whole blood and 4 ml of serum drawn. This time point is incorrect and has been moved to Week 15. At Week 15, subjects will have at least 51 ml of whole blood and 4 ml serum drawn. This change is due to immunologic markers and for the purpose of expected responses at these designated time points.

7. Section 6.2 Before Treatment Procedures indicates that subjects who consent to participate will have biopsy slides or paraffin-embedded tissue block(s) from a previous biopsy visit and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the PAC. This language has been updated to say: Subjects who consent to participate must have paraffin-embedded tissue block(s) from a previous biopsy visit and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the PAC.
8. Section 7.12.1 Adverse Events of Special Interest: the following sentence was added: As per the Toxicity Grade for Healthy Adults, the most severe grade for that particular event is to be documented in the CRFs.
9. Section 12.2 Pathology Adjudication Committee: This section has been updated to remove procedural content from the protocol and allow individuals to reference the PAC Charter document.
10. The ICF blood sample amount has been updated to reflect the new amount drawn throughout the study which will be about 221ml.

Medical Monitor Approval Page

Drug: VGX-3100

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

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

Approval Signature:

[redacted] _____ [redacted] _____
Inovio Pharmaceuticals Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board/Ethics committee approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 (IRB/IEC) 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 International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

<Insert Principal Investigator Printed Name>	Date (dd/Mmm/yyyy)

Site Number: _____

Site Name: _____

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal High-Grade Squamous Intraepithelial Lesions, HSIL (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2
Protocol Number: HPV-203
Trial Phase: 2a
Estimated Number of Trial Centers and Countries/Regions: Approximately 5 study centers located in North America
Formulation: VGX-3100
Trial Design: Multi-center, single-arm, open-label phase 2 study
Criteria for Evaluation: To provide a treatment to regress anal or anal/peri-anal HSIL and clear the related HPV-16 and/or HPV-18 (HPV16/18) in individuals that are seronegative for HIV-1/2. **Research Hypothesis:** VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal HSIL[1], (AIN2[2], AIN3[3], PAIN2[4], PAIN3[5]) associated with HPV-16 and/or HPV-18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.
Dose of VGX-3100: 6 mg (1mL)
Administration: Intramuscular injection followed by EP
VGX-3100 Dosing Schedule: Day 0, Week 4 and Week 12 with one additional dose given to partial responders at Week 40
Study Duration: 88 Weeks
Primary Objective: Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18.
Primary Endpoint: Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL[6] on histology (i.e., collected via biopsy or excisional treatment)[7] and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue.

[1] High-grade Squamous Intraepithelial Lesion
[2] Grade 2 Anal Intraepithelial Neoplasia
[3] Grade 3 Anal Intraepithelial Neoplasia
[4] Grade 2 Peri-anal Intraepithelial Neoplasia
[5] Grade 3 Peri-anal Intraepithelial Neoplasia
[6] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.
[7] A treatment responder is defined as a subject with no histologic evidence of anal or anal/peri-anal HSIL and no evidence of HPV-16 or HPV-18 in anal lesion tissue and who did not receive any non-study treatment of curative intent of intra-anal and/or peri-anal lesions. A treatment non-responder is defined as a subject with histologic evidence of anal or anal/peri-anal HSIL, adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma or a subject with evidence of HPV-16/18 in anal lesion tissue or a subject who received non-study treatment of curative intent of intra-anal and/or peri-anal lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC). 1b. **All** adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study (through the Week 88 visit)
2. Determine the **efficacy** of three doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL[8] on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
3. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue	3. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18[9] from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
4. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal tissue swab testing	4. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
5. Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue	5. Proportion of subjects with **no evidence** of anal or anal/peri-anal Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
6. Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL	6. Proportion of subjects with **no progression**[10] of anal or anal/peri-anal HSIL to carcinoma from baseline to histology (i.e. biopsies or excisional treatment) at the Week 36 visit
7. Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in size of peri-anal lesion(s) if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36	7. Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s), as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline[11]. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy

	photographic imaging of qualifying lesion(s)[12] at Weeks 36, 64, and 88 compared to baseline[11].
8. Determine the humoral and cellular immune response following dose 3 and additional time points compared to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline and the Weeks 15, 36, 64, and 88 visits 8b. Interferon-γ ELISpot response spot forming units (SFU) at baseline and the Weeks 15, 36, 64, and 88 visits 8c. Flow Cytometry response magnitude at baseline and Week 15 visit

[8] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.

[9] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.

[10] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.

[11] Baseline photographic imaging is defined as photographs obtained pre-biopsy at Screening, or post biopsy at Screening (for subjects with historical biopsy tissue).

[12] An intra-anal and/or peri-anal lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed anal or anal/peri-anal HSIL by the Pathology Adjudication Committee (PAC).

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16 and/or HPV-18	1. Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
2. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
3. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18	3. Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
4. Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples	4. Assessment of proinflammatory and immunosuppressive elements in tissue, where feasibile.[13]
5. Describe the **clearance** of HPV-16 and/or HPV-18 infection from non-anal anatomic locations	5. Proportion of subjects who have **cleared** HPV-16 and/or HPV-18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
6. Evaluate the effect of Human Leukocyte Antigen (HLA) type on **efficacy**	6. HLA (per-locus and per-allele basis) in conjunction with **histologic regression** of anal or anal/peri-anal HSIL at the Week 36 visit
7. Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression	7. HRA, cytology, and HPV test results and miRNA profile (baseline and at the Weeks 15 and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit
8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100	8. Patient reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88.

	There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose.

[13]Additonal assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possible other relevant markers identified in the literature as sample allows.

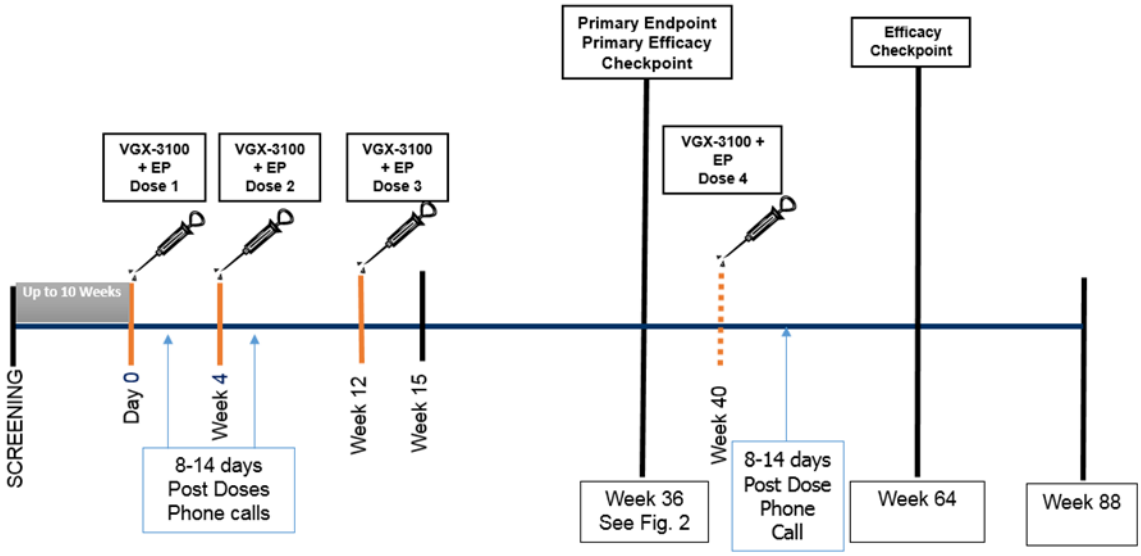
Study Design:

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or HPV-18.

Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40.

All subjects are scheduled to be followed to Week 88.

Figure 1: HPV-203 Study Visit Schedule



Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Subjects must also have intra-anal and/or peri-anal lesion(s) tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

Visualization of the lesion and digital anal rectal examination (DARE) alone are insufficient evidence to confirm disease regression. Disease regression will be primarily based on histopathologic assessment at Week 36 and additionally assessed at Week 64. Subjects will be monitored during the course of the study by DARE and HRA. Intra-anal lesion(s) will be assessed at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 using HRA. Standardized high resolution digital imaging will be used to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Weeks 36, 64, and 88 compared to baseline..

The decision process following the results of the Week 36 biopsy are described below in ***Figure 2*** and are as follows: At Week 36, the subject will undergo repeat intra-anal and/or peri-anal punch biopsies of all HSIL lesions confirmed by the PAC at Screening of adequate size (≥ 4mm). (See **Table 1** for Minimally Required Biopsy Procedures). If after evaluation of the biopsy tissue(s) by the PAC there is no evidence of HSIL (defined by Subgroups A or B), the subject will continue to Week 64 for HRA and undergo biopsies of the same areas (HSIL lesions) as the baseline biopsies.

Figure 2: Decision process at Week 40

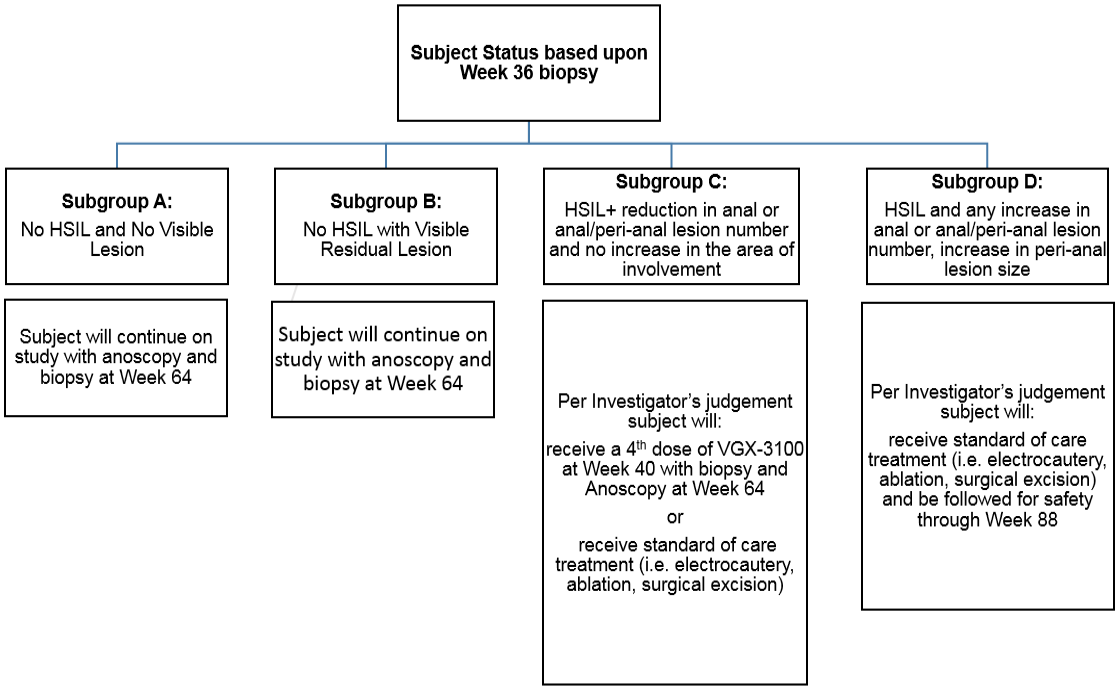


Table 1: Minimally Required Procedure at each Biopsy Visit

Pre-biopsy High Resolution Anoscopy Finding	Minimally required procedure
No lesion	Punch biopsy and photography; biopsy should be collected from within the approximate original boundaries of the study entry HSIL as proximal as possible to the original biopsy site which was previously determined to be HSIL by the PAC.
Single lesion (which was also present at baseline)	Punch biopsy and photography; biopsy should be collected within the boundaries of the original lesion and from the area most suspicious for advanced disease within the lesion by clinical exam.
Multiple lesions	Punch biopsies and photography; biopsy should be collected from the same lesions diagnosed as HSIL from study entry and from the area most suspicious for advanced disease within the lesion by clinical exam.

If HSIL is diagnosed in any Week 36 biopsy, but there is a reduction in the number of intra-anal and/or peri-anal lesion(s), reduction in peri-anal lesion(s) size or no change in peri-anal lesion(s) size from baseline (defined by Subgroup C), the Investigator has the option to administer a 4th dose of VGX-3100 at Week 40, and the subject will continue on the study to have HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may instead choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of standard of care.

In the event of worsening anal or anal/peri-anal HSIL at any time during the trial (defined as any increase in lesion(s) area from baseline or worsening of anal or anal/peri-anal HSIL to cancer), the subject may receive standard of care treatment (i.e. electrocautery, ablation, surgical excision) per the Investigator's judgment but will continue on the study through Week 88 with HRA, but without further biopsy unless it is part of the standard of care.

If there is histologic progression to carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment but will continue through Week 88 with HRA, but without further biopsy unless it is part of the standard of care. The event will be reported as an SAE per Section 7.3. If wide excision is required, the sample(s) obtained will be sent to the PAC for evaluation.

Efficacy Assessment:

Screening biopsies will be collected from all intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm). Visible lesion(s) observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and/or HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal tissue, utilizing HRA with biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Tissue samples will be analyzed for evidence of histopathologic regression. Clearance of HPV-16 and/or HPV-18 will be determined using the type specific HPV PCR test SPF10 on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be collected at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using Cobas HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) rinse samples will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy.

Immunogenicity Assessment: Humoral and cell mediated immune responses to VGX-3100 may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, 64, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

Virologic Assessment: Intra-anal and/or peri-anal swabs will be obtained to characterize HPV infection at Screening, Day 0, and Weeks 4, 15, 28, 36, 64 and 88 by PCR™ Cobas. Likewise, PCR-based assessment of histological samples will occur at Screening and Weeks 36 and 64.

For testing of non-anal sites, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) samples (all subjects) will be obtained to characterize HPV infection at Day 0, and at Weeks 4,15, 28, 36, 64 and 88.

HLA haplotyping: A PBMC sample from any sample collected during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Safety Assessment: Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the Participant Diary Card (PCD).
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed to Week 88.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. Refer to Section 3.8 for stopping rule criteria.

Definition of Responder and Non-Responder for Primary Endpoint:

Responder and non-responder definitions (**Table 2**) take into account both histopathologic regression of anal or anal/peri-anal HSIL and virologic (HPV-16/18) clearance as measured by intra-anal and/or peri-anal tissue since HPV persistence is an important factor in the clinical progression of HSIL. Any case of histologically confirmed progression from HPV-16/18 positive anal or anal/peri-anal HSIL to carcinoma is considered a non-responder.

Table 2: Definition of Responder and Non-Responder for Primary Endpoint

Responder	Non-Responder
No histologic evidence of anal or anal/peri-anal HSIL AND Negative PCR for HPV-16 or HPV-18 in anal lesion tissue AND No non-study treatment of curative intent of intra-anal and/or peri-anal lesions	Histologic evidence of anal or anal/peri-anal HSIL, anal Adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma OR PCR positive for HPV-16 or HPV-18 in anal lesion tissue OR Any non-study treatment of curative intent of intra-anal and/or peri-anal lesions

Study Population:
Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2 within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16 and/or HPV-18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue specimens/slides provided to the Study Pathology Adjudication Committee (PAC) for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    a. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    a. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40mIU/mL;
    b. Surgically sterile due to absence of ovaries or due to bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    c. Subject agreement to avoid pregnancy for one month after last dose (Week 12 or Week 40);
    d. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of investigational product (Week 12 or Week 40). The following are acceptable methods:
        i. Hormonal contraception: either combined progestin-alone including oral contraceptive, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g. deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;
9. Men who would father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

Exclusion:

1. Untreated micro invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN;
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have completed and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator;
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    c. Long-term use (≥7 days) or oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, otic, nasal, topical, 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. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks of any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
17. 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 the study results (e.g. chronic renal failure, angina, myocardial ischemia or infarctation, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of Day 0;
20. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
21. 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;
22. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent form (participating in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrillator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or evaluation of any study product;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military personnel;
    d. Study-related staff or family members of study-related staff

TRIAL SCHEDULE OF EVENTS

Table 3: Schedule of Events

Study Action	Screen (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Informed consent	X												
Medical History/Demographics	X												
Medications (prior/concomitant)	X	X		X		X	X	X	X	X		X	X
Socio-behavioral assessment	X								X			X[o]	X
Inclusion/Exclusion criteria[1]	X	X											
Physical exam (PE)/assessment [a]	X	X		X		X	X	X	X	X		X	X
Vital signs	X[b]	X		X		X	X	X	X	X		X	X
Screening safety (12 lead ECG, laboratories) [c]	X												
Pregnancy Testing [d]	X	X		X		X	X	X	X	X		X	X
HIV Ab by ELISA	X								X				
Blood immunologic samples	X[e]	X[e]					X[f]		X[e]			X[e]	X[e]
HLA testing [g]	X												
Oropharyngeal (OP) rinse		X		X			X	X	X			X	X
Vaginal, cervical, and penile swab		X		X			X	X	X			X	X
Intra-anal and/or peri-anal swab	X	X		X			X	X	X			X	X
Digital Anal Rectal Examination DARE [h]	X	X		X			X	X	X			X	X
High Resolution Anoscopy (HRA) [i]	X	X		X			X	X	X			X	X
Lesion photography [j]	X	X		X			X	X	X			X	X
Biopsy [k]	X								X			X	
Inject VGX-3100 +EP[l]		X		X		X				X[l]			
Post treatment reaction assessment		X		X		X				X			
Distribute Participant Diary Card (PDC)		X		X		X				X			
Review PDC [m]			X		X		X				X	X	
Patient Reported Outcomes (PROs) (SF-36v2™) (EQ-5D-5L) [n]		X[p]	X	X	X	X	X		X	X	X[q]	X	X

[1] Subject eligibility will be reconfirmed at every visit.

[a] Full Physical exam (PE) mandatory at Screening and study discharge (Week 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE.
[b] Screening vital signs must include a measured height and weight and calculated body mass index (BMI) (Bodyweight in kilograms divided by height in meters squared). Weight will be collected at all dosing visits.
[c] Screening 12-lead Electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, alanine aminotransferase (ALT), and Creatine Phosphokinase (CPK) performed within 45 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required for female subjects at Screening, prior to each study treatment, high-resolution anoscopy (HRA), and biopsy/surgical excision; the pregnancy test at Week 40 would only be needed for subjects who receive an additional dose.
[e] At least 34 mL (4 x 8.5 mL yellow (ACD) tubes) whole blood and 4 mL serum per time point. At least 68 mL whole blood and 8 mL serum should be collected prior to first dose.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15.
[g] Human Leukocyte Antigen (HLA) testing will be performed once from an existing Peripheral Blood Mononuclear Cells (PBMC) sample.
[h] Digital Anal Rectal Examinations (DARE) are to be performed once cytology has been collected and prior to HRA.
[i] An additional visit may be scheduled to perform HRA if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening) and Weeks 36 and 64 for Subgroup C unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the Pathology Adjudication Committee (PAC) for review.
[j] Photography of qualifying lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. Photographs of peri-anal lesion(s) will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Weeks 36, 64, and 88 compared to baseline.
[k] Tissue specimen and slides from all excised tissue lesion(s) that led to eligibility at study entry must be reviewed by the PAC and residual tissue from entry and Weeks 36 and 64 specimen(s) (paraffin blocks) must be sent to the central laboratory for immune analysis and Human Papillomavirus (HPV) testing.
[l] Potential dosing at Week 40 is applicable for partial responders only.
[m] A phone call will be used to review the Participant Diary Card (PDC) with subject within 8-14 days following doses 1 and 2. The patient will be expected to bring the PDC to the next visit for review. Subjects who receive an additional 4th dose will have a phone call 8-14 days post dose 4 where the PDC will be reviewed.
[n] Patient-reported outcome (PRO) measures (SF-36v2™ and the EQ-5D-5L), plus two additional "global" questions will be assessed as described in Section 6.13.
[o] This socio-behavioral assessment will only apply to those subjects in Subgroup C who receive a 4th dose of investigational product.

[p] PROs must be administered prior to first dose of study drug.
[q] PROs will only be for subjects who received a 4th dose of study drug.

1.0 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. Human Papillomavirus 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). In the United States (US), approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type (HR-HPV) and thus can cause cancer [2]. In U.S. adults through age 59 years, about 25% of men and 20% of women have genital HR-HPV infection [3]. Human Papillomavirus causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV Deoxyribonucleic Acid (DNA) was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (OP), 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS) [4]. An average of over 30,000 cases per year of HPV-attributable cancer were diagnosed during the period 2008 through 2012 in the U.S. [5]. Human Papillomavirus-16 and HPV-18 are the most significant among high-risk types since they are responsible for most HPV-caused cancers [4].

With regard to anal cancer, about 95% of cases are caused by HPV, and most of those cases are caused by HPV-16 [6, 7]; with some by HPV-18 and perhaps other HPV genotypes [2]. An estimated 8,200 new cases of anal cancer in the US are diagnosed each year (for year 2017), with an estimated 1,100 deaths annually due to this cancer [8]. In Canada, the latest available data is for year 2013, during which 580 new cases of anal cancer were diagnosed and 144 persons died due to anal cancer [9].

The precursor lesion to HPV-associated anal cancer historically was known as anal high-grade dysplasia or intraepithelial neoplasia. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term HSIL to encompass high grade dysplasia [10]. Among HPV-associated anal HSIL cases in the US, about 55% to 80% are associated with HPV-16/18, and worldwide about 80% of cases are associated with HPV-16/18 [7, 11, 12].

Left untreated, anal HSIL may progress to cancer. Spontaneous regression of these lesions may occur, but the available data indicate that such regression is in the minority of cases. For example, published results of a small observational study of anal HSIL in men who have sex with men (MSM) in Australia found spontaneous regression occurred in 29% of those HIV-negative after more than one year of follow-up time, with an even lower regression rate in those who were HIV-positive. That study also found that the majority (71%) of patients who regressed only did so to anal low-grade SIL (Low grade squamous intraepithelial lesion [LSIL]), with the remainder to normal tissue [13]. In an ongoing larger observational study of gay and bisexual men – the Study of the Prevention of Anal Cancer (SPANC) [14] -- also comprised of patients HIV-negative and HIV-positive (though with medically well-controlled CD4 cell counts), preliminary published data show that 55% of patients with anal HSIL, regardless of HIV status, had their HSIL persist to at least 12 months and HPV-16 was significantly associated with persistence as compared to other HPV genotypes (Relative Risk of 1.5) [15].

Spontaneous regression data from that study are not yet published, but preliminary data show spontaneous regression of only about 20% by one year of follow-up. Further, many of those patients who regressed later recurred to HSIL, suggesting that HSIL in some cases may be merely regressing to a level below the detection limit but is still present [16]. Other published data from a sub-study of that larger study indicate that HPV-16 E6-specific T-cell responses may be associated with recent anal HSIL regression (Pexact = 0.065) [17]. That finding provides further plausibility, in addition to other data summarized later in this protocol, that VGX-3100 plus electroporation treatment could cause anal HSIL regression.

Anal HPV infection spontaneous clearance in non-immunocompromised adults can occur, but such data are generally unavailable for persons who have anal HSIL. Nevertheless, high-risk HPV (HR-HPV) clearance by one year ranges from 56% to 78%, varying by gender and sexual preference etc., as found in large, prospective studies [18-20] with some wider variation in clearance rates for HPV-16 and HPV-18 specifically in those studies.

Collectively, the aforementioned anal HSIL regression and HPV clearance data comprise in part the historical control data that the results of the present trial will be compared to.

1.1.1 VGX-3100

VGX-3100 contains plasmids that target HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated Investigational Product (IP) designed as a non-surgical treatment of HPV-16/18-related anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, and PAIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was Water for Injection (WFI) with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This frozen formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100 was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This non-frozen formulation of VGX-3100 was administered to 117 subjects in a Phase 1 clinical trial, HPV-101 in which subjects were randomized 1:1 to receive the non-frozen or frozen formulation of VGX-3100. In study HPV-101, healthy adults received three 6 mg IM doses of VGX-3100 in the frozen or non-frozen formulations followed by EP with the CELLECTRA™ 5Pdevice. The non-frozen formulation was found 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 enzyme-linked immunospot (ELIspot) assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (frozen formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16/18 [1]. The Phase 2b study, HPV-003, enrolled 169 subjects with high grade cervical dysplasia from seven countries and one US Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, US and Puerto Rico). Subjects were randomized in a 3:1 ratio to treatment with VGX-3100 or placebo, respectively. All

subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or Loop Electrical Excision Procedure (LEEP) of the cervix at Week 36 to assess efficacy defined as regression of high grade Cervical Intraepithelial Neoplasia (CIN) by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to Grade 1 Cervical Intraepithelial Neoplasia (CIN1) or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol (PP) and modified Intent to Treat (mITT) analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.2 ELECTROPORATION

CELLECTRA® 2000 & CELLECTRA™ 5PSP are both electroporation (EP) devices developed by INOVIO. Electroporation with CELLECTRA™5PSP 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 [21, 22]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced immunogenicity by 10 to 100 fold [23, 24]. 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 [21]. 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) [22, 23].

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 U.S. 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-16/18 related 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.

Inovio Pharmaceuticals Inc. device experience demonstrates that delivery of its proprietary electroporation pulses into muscle immediately following injection of DNA plasmids (including VGX-3100) is well-tolerated in humans and no significant safety issues have been identified [1, 22, 24]. For further information concerning the CELLECTRA™ 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.3 DOSE RATIONALE

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

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 (AEs) from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in HPV-003, Phase 2b study. The results obtained in the phase 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 2 trial [1].

1.2 POTENTIAL BENEFITS

Currently accepted surgical treatments are associated with a high recurrence rate, >50%. The current surgical approaches also have risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the anus. This study has been designed to provide non-surgical treatment with an aim of regression of the anal or anal/peri-anal HSIL and thus avoiding the need for surgical excision, infrared coagulation, electrocautery and laser therapy. In the absence of complete resolution of intra-anal and/or peri-anal lesions, there would still be potential benefit from a partial response, which would reduce or minimize the need for excisional or ablative treatment modalities. The other potential benefit is that the response to VGX-3100 is systemic and may clear the underlying HPV infection, which is the root cause. Consequently, there is the potential to reduce the risk of recurrence of anal or anal/peri-anal HSIL.

1.3 POTENTIAL RISKS

Risks associated with VGX-3100 for the treatment of anal or anal/peri-anal HSIL are injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience with VGX-3100 with healthy volunteers and in women with cervical HSIL, 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 anal dysplasia and possible missed diagnosis of an occult early invasive cancer for the VGX-3100 non-responders, who do not spontaneously regress. Although professional guidelines typically advocate excisional therapy for adults with HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [10]. The risk of a missed diagnosis of an occult early invasive cancer exists for all current treatment modalities including surgical and ablative therapies. To mitigate these potential risks the study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult

early invasive cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent High-resolution anoscopy (HRA) and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced physicians, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

An independent Data and Safety Monitoring Board (DSMB) will also advise the Sponsor if it appears that the frequency of regression is unacceptably low. These measures should minimize the risk of progression of the HSIL and the risk of harboring an undiagnosed occult early invasive cancer.

In the HPV-003 study of women with cervical HSIL, 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 and even lower than the 6.7% that has been reported under standard of care settings [18].

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

2.0 PURPOSE AND HYPOTHESIS

2.1 PURPOSE

To provide a treatment to potentially regress and clear HPV-16/18 related anal or anal/peri-anal HSIL in individuals that are seronegative for HIV-1/2.

2.2 HYPOTHESIS

VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal high-grade squamous intraepithelial lesions, HSIL, (AIN2, AIN3, PAIN2, PAIN3) associated with HPV-16/18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.

3.0 TRIAL DESIGN AND ENDPOINTS

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or 18. Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40. All subjects are scheduled to be followed to Week 88.

To be eligible for the study, subjects must consent to participate and agree to the collection of anal lesion tissue samples for anal cytology and genotyping, a Digital Anal Rectal Examination (DARE), blood samples for immunologic and Human Leukocyte

Antigen (HLA) assessments, HRA and HRA guided biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening.

Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Subjects must also have intra-anal and/or peri-anal lesion tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

3.1 PRIMARY OBJECTIVE(S)

Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16/18

3.2 PRIMARY ENDPOINT(S)

Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL on histology (i.e., collected via biopsy or excisional treatment) and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue

3.3 SECONDARY OBJECTIVE(S)

- Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by testing from lesion tissue
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by intra-anal tissue swab testing
- Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in the size of peri-anal lesion(s), if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36
- Determine the humoral and cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline

3.4 ASSOCIATED SECONDARY ENDPOINT(S)

- Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC)
- **All** AEs including Serious Adverse Events (SAES), unanticipated (serious) adverse device effect (UADE), and other unexpected AEs for the duration of the study (through the Week 88 visit)
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
- Proportion of subjects with **no evidence** of anal or anal/peri-anal LSIL or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, and PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36
- Proportion of subjects with **no progression** of anal or anal/peri-anal HSIL to carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
- Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s) and the size of peri-anal lesion(s) if present, as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline. For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying lesions at Weeks 36, 64, and 88 compared to baseline
- Levels of serum anti-HPV-16 and anti-HPV-18 antibody (Ab) concentrations at baseline and the Weeks 15, 36, 64, 88 visits
- Interferon- γ ELISpot response magnitudes at baseline, and the Weeks 15, 36, 64, and 88 visits
- Flow Cytometry response magnitudes at baseline and Week 15 visits

3.5 EXPLORATORY OBJECTIVE(S)

- Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16/18
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16/18
- Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples
- Describe the **clearance** of HPV-16/18 infection from non-anal anatomic locations

- Evaluate the effect of HLA type on **efficacy**
- Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression
- Describe PRO for subjects treated with VGX-3100

3.6 ASSOCIATED EXPLORATORY ENDPOINT(S)

- Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
- Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
- Assessment of proinflammatory and immunosuppressive elements in tissue, where feasible.
- Proportion of subjects who have **cleared** HPV-16/18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
- HLA (per-locus and per-allele basis) in conjunction with **histologic regression** of anal or anal/peri-anal HSIL at Week 36 visit
- HRA, cytology, and HPV test results and miRNA profile (baseline and at Weeks 15, 28, and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit
- Patient reported outcome endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose.

3.7 EFFICACY ASSESSMENT

Screening biopsies will be collected from all intra-anal and/or peri-anal lesions of adequate size (≥4mm). Visible lesions observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal and/or peri-anal tissue obtained from biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects

disease progression. Tissue will be analyzed for evidence of histopathologic regression. Clearance of HPV-16/18 will be determined using the by type specific HPV polymerase chain reaction (PCR) test SPF10 on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0 (prior to dosing) and Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using Cobas HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects) and OP rinse samples (all subjects) will be obtained at Day 0 (prior to dosing), and at Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of the standard of care. All tissue samples obtained from biopsies or removed per standard of care will be sent to the PAC for review.

3.8 SAFETY ASSESSMENT

Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the PDC.
2) All AEs including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed for 88 weeks.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. The following stopping rules will be applied:

- If at any time during the study one-third (1/3) or more of the subjects experience an Adverse Event of Special Interest (AESI), further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AEs) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 AEs, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- The Sponsor or Designee will notify all Investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

3.9 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100 treatment may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

4.0 TRIAL POPULATION

4.1 INCLUSION CRITERIA

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2 within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16/18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue specimen/slides provided to the Study PAC for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    i. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    i. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with follicle-stimulating hormone (FSH) level >40mIU/mL;
    ii. Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    iii. Subject agreement to avoid pregnancy one month after last dose of IP (Week 12 or Week 40);

iv. Women of Childbearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of IP (Week 12 or Week 40). The following are acceptable methods:

1. 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);
2. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
3. Intrauterine device or intrauterine system;
4. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;

9. Men who could father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

4.2 EXCLUSION CRITERIA

1. Untreated micro invasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN;
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;

10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator;
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    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, nasal, topical, 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 Tumor Necrosis Factor (TNF)-α inhibitors (e.g. infliximab, adalmumab or etanercept);
    e. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks of any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treated as deemed by the Investigator;
17. 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);
18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of a study dose;
20. History of seizures unless seizure free to 5 years with the use of one or fewer antiepileptic agents;
21. 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;

22. Resting heart rate <50 beats per minute (bpm) (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing the ICF (participation in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrilator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. 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;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntary incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military service personnel;
    d. Study-related staff or family members of study-related staff

4.3 DISCONTINUATION/WITHDRAWAL OF TRIAL SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION FROM THE STUDY

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from further treatment with VGX-3100. Subjects will not receive further doses of VGX-3100 followed by EP but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests a Grade 3 toxicity attributable to VGX-3100/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM STUDY

Subjects who become ineligible to continue on the study based on no longer meeting the inclusion criteria should be discontinued from study treatment and managed per routine standard of care but should continue on the study without further biopsy.

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 anal or anal/peri-anal HSIL, and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls to the subject should be made and if that fails, then a certified letter is sent to the subject's last known mailing address) so that they can be considered withdrawn from the study for disposition purposes. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will the subject be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

If a subject elects to discontinue treatment/EP they should be encouraged to stay in the study and complete all follow-up visits and procedures and have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events (Table 3). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 88). A subject will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs and/or SAES present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 – Safety Parameters.

4.3.4 REASONS FOR DISCONTINUATION/WITHDRAWAL

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

- 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 AEs regardless of relation to study drug.
- Death of a subject, (including manner of death if known)
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the eCRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a maternal obstetrical or medical need to withdraw subject.

Investigator must consult the Medical Monitor before withdrawing a subject from participation in the study.

- Protocol Deviation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g. treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including 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 who receive study treatment and discontinue prior to Week 36, primary endpoint procedures, then supplementation of study subjects will be considered.

5.0 TRIAL TREATMENT

5.1 INVESTIGATIONAL BIOLOGIC PRODUCT

The IP to be used in this trial is described in Table 4. The IP will be presented in a clear glass cartridge and injected intramuscularly.

Table 4: Investigational Biologic Product

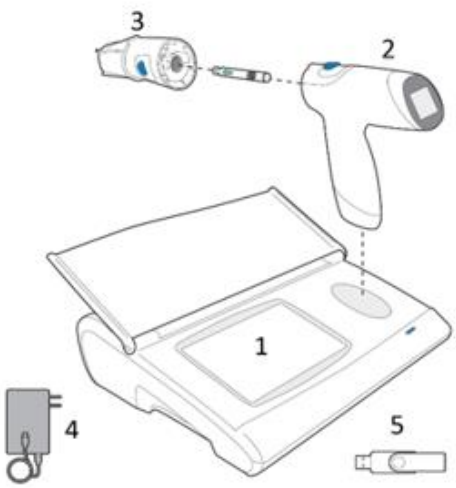
Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL

5.2 CELLECTRA™ 5PSP DEVICE DESCRIPTION:

VGX-3100 will be delivered using the CELLECTRA™5PSP device. The device consists of five (5) main components (see

Figure 3).

Figure 3: CELLECTRA™5PSP Base Station with Handset



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

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

3) CELLECTRA™ 5PSP Sterile Single Use Array which consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

4) USB International Power Supply

5) Flash Drive

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset.

Handset

The handset facilitates delivery of the needles for injection and electroporation into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit and is compliant to International Ethics Committee (IEC) 62133 and UL 2054. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire.

Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 IM injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array

(indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The 5PSP Array features no software.

The base station and handset with the 5PSP Array are illustrated in

Figure 3.

5.3 TREATMENT REGIMEN

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-203 study will receive the same three 6 mg doses of VGX-3100 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 at Week 12. A fourth dose may be administered at Week 40.

The first study treatment will be given as soon as possible following confirmation of anal or anal/peri-anal 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.

5.4 PACKAGING AND HANDLING

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, single-panel label with tear-off. The VGX-3100 label will include, at minimum, the following information in Table 5.

Table 5: Example of Packaging and Label Information

Cartridges (primary container)	**Pouches** (secondary packaging)
LABEL VGX-3100 Insert cap end Sponsor name IM administration Investigational Use Only	**LABEL BODY** Study ID VGX-3100 Single-use cartridge containing 1 mL IM administration via CELLECTRA™ 5PSP Store at 2-8°C, expiration date Caution Statement Sponsor name and address
	LABEL TEAR OFF Study ID VGX-3100 Patient ID: _____ Date: (DD-MMM-YYYY): _____ Must be used by (time): _____

See Figure 4 below for example of CELLECTRA™ 5PSP device component labels.

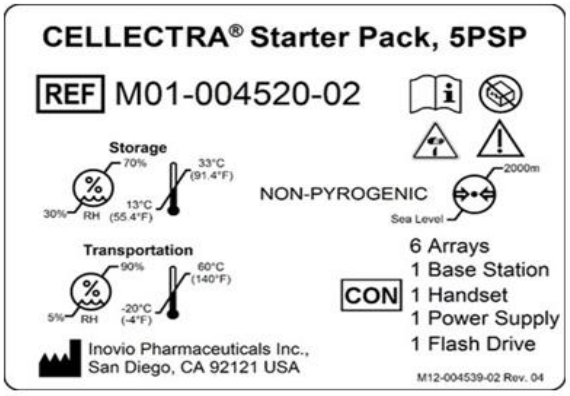
Figure 4: Examples of Device Labels (Base, Handset, Array, Outer Box)

Base Station Label

Handset Label

5PSP Array Label

Outer Box Packaging Label



5.5 HANDLING AND STORAGE OF IP AND DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual. The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and relative humidity ranges of 30-70%. The Sponsor should be notified of any deviations from this recommended storage condition.

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. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. The Sponsor should be notified of any deviations from this recommended storage condition. Inovio Pharmaceuticals Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. For the specific

temperature guidelines for storing, please refer to the CELLECTRA™ 5PSP User Manual.

5.6 PREPARATION AND DISPENSING

It is the responsibility of the Investigator to ensure that VGX-3100 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, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration.

The pouch must not be discarded until:

1. Administration is completed and
2. All pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator. If VGX-3100 is not used within this timeframe it must be discarded after reconciliation.

5.7 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of the 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. Refer to the User Manual for further instruction. 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.

5.8 DRUG AND DEVICE ACCOUNTABILITY

5.8.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of IP 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;
- Date and initials of person responsible for each IP inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;

- Amount destroyed at study site, if applicable

5.8.2 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The site is responsible for maintaining the device. The device must have full traceability from receipt of the products through the subject use, and the return of the device. The site must document acknowledgement of receipt and then notify INOVIO upon receipt of the device. This includes the content shipped and condition of the items upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP Base Station & Handset serial number, 5PSP 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.

5.9 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT AND CELLECTRA™ 5PSP DEVICE

5.9.1 RETURN OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at the site per the institutions policy or returned to INOVIO or its designee, if the site cannot destroy the unused IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site. Do not attempt to remove the cartridge from the array once it has been used.

It is the Investigator's responsibility to arrange for the 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 personal or designated Study Monitor.

If IP is returned to INOVIO, 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. The return of unused IP(s) should be arranged with the responsible INOVIO personnel and/or Clinical Monitor.

5.9.2 RETURN OF CELLECTRA™ 5PSP DEVICE

Upon completion or termination of the study, all investigational devices and unused components (Base, Station, Handset, and 5PSP Arrays) must be returned to INOVIO.

All device components returned to INOVIO 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.

If any component is to be 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, 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.

6.0 TRIAL 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 3).

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

Protocol waivers or exemptions will not be granted. 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 3) are essential and required for study conduct. Subject eligibility should be reconfirmed at every study visit.

6.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial subjects, explain the trial, and provide them with an ICF that describes the Screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial 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 trial 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.

6.2 BEFORE TREATMENT PROCEDURES

Subjects who consent to participate must have paraffin-embedded tissue block(s) from a previous biopsy and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the 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), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with anal or anal/peri-anal HSIL, by a local pathologist, where the initial biopsy tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, an additional biopsy sample should be collected during Screening following the consent of the subject. The 10 week Screening window begins upon collection of the biopsy sample that will be evaluated by the PAC.

At Screening, subjects must have a diagnosis of histologic anal or anal/peri-anal HSIL confirmed by the PAC and intra-anal and/or peri-anal specimen test positive for HPV-16/18 by PCR to be eligible for participation in the study (provided the subject also

meets other eligibility criteria). Subjects whose intra-anal and/or peri-anal specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16/18.

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

6.2.1 SCREENING EVALUATIONS

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the safety laboratory collections/assessments, which must be performed within 45 days prior to Day 0. All Screening assessment values must be reviewed ***prior*** to study treatment. Some of these evaluations/actions will be performed again later in the trial (see later text and the Schedule of Events Table 3 for more detail).

- Signed ICF
- Medical history/demographics, including history of prior anal or anal/peri-anal HSIL
- Socio-Behavioral Assessment; including smoking history, exposure to second-hand smoke, alcohol intake history, recreational drug use and contraceptive use
- Prior concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Complete Physical Examination
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate), height, weight and body mass index (BMI) measurements
- 12-lead ECG (within 45 days prior to Day 0)
- Baseline laboratory evaluations (including complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine (Cr), glucose, alanine aminotransferase [ALT], and creatine phosphokinase [CPK]) (to be performed within 45 days prior to Day 0)
- Urine pregnancy test
- Serology (HIV Ab) within 30 days prior to Day 0
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- Digital Anal Rectal Examination (DARE)
- High Resolution Anoscopy (HRA)
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (slides from all excised tissue must be reviewed by the PAC).
- Whole blood (at least 68 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile

6.3 DURING TREATMENT PROCEDURES BY VISIT

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

6.3.1 DAY 0

The following study evaluations will be performed at Day 0 (unless noted) prior to the first study treatment:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcome (SF-36v2™ and EQ-5D-5L) (may be performed at Day -1 or on Day 0, again provided it is done prior to the first study treatment)
- Study treatment administration

The following evaluations will be performed on Day 0 after study treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during the phone call:

- Review Day 0 of 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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.3 WEEK 4 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant mediation review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient report outcomes (SF-36v2™ and EQ-5D-5L)
- Collect PDC for dose 1
- Study treatment administration

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

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

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during the phone call:

- Review of PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.5 WEEK 12 (± 4 DAYS)

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

- Reconfirm subject eligibility

- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect and review PDC for dose 2
- Study treatment administration

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

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.6 WEEK 15 (± 1 WEEK)

The following study evaluations will be performed at Week 15:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.7 WEEK 28 (± 1 WEEK)

The following study evaluations will be performed at Week 28:

- Reconfirm subject eligibility

- Concomitant medical review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)

6.3.8 WEEK 36 (± 1 WEEK)

The following study evaluations will be performed at Week 36:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.9 WEEK 40 (± 1 WEEK)

The following study evaluations will be performed at Week 40:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Study treatment administration
- Based on biopsy results collected at Week 36 and Investigator judgment, a 4th dose may be given at this visit

****Please remember to download EP data from CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

The following study evaluations will be performed at the Week 40 post treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment;
- Distribute PDC
- Patient reported outcomes-only the two "global" questions for this visit

6.3.10 8-14 DAYS POST DOSE 4 PHONE CALL (FOR SUBJECTS WHO RECEIVED A 4TH DOSE)

The following information will be evaluated during the phone call:

- Review PDC for dose 4 (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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.11 WEEK 64 (± 2 WEEKS)

The following study evaluations will be performed at Week 64:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment (only for subjects who received a 4th dose at Week 40)
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse

- Vaginal, cervical and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.12 WEEK 88 (± 2 WEEKS)

The following study evaluations will be performed at Week 88:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Urine pregnancy test
- Vital signs
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.4 TRIAL PROCEDURES

6.5 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all trial-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., ANUS01001). 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.

6.6 DEMOGRAPHICS

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

- Age
- Gender
- Race/ethnicity
- Dominant hand/arm

6.7 SAFETY EVALUATIONS

6.7.1 PHYSICAL EXAM

A full Physical exam (PE) will be conducted during Screening and study discharge (Week 88). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems, and a DARE. All assessments not completed should be marked as not done.

A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

6.7.2 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 prior to measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.7.3 HEIGHT AND WEIGHT

Weight and height will be collected at all dosing visits in order to calculate the BMI.

6.7.4 MEDICAL HISTORY

Medical history, including history of prior anal or anal/peri-anal dysplasia and gynecologic history will be obtained at Screening. For females, previous history of treatment for VIN, CIN and/or VAIN will be collected. All relevant past and present conditions, as well as prior surgical procedures at least 6 months prior to enrollment will be recorded for the main body systems.

6.7.5 SOCIO-BEHAVIORAL ASSESSMENTS

Socio-Behavioral Assessment, including self-reporting of the following: smoking history, history of exposure to second-hand smoke, alcohol intake history, recreational drug use history, history of contraceptive use and type of contraceptive if known, reproductive history, sexual preference and sexual practices history, and pregnancy history will be obtained at Screening.

At Weeks 36, 64, and 88, a socio-behavioral assessment will be performed again to document any changes from Screening and/or other time periods.

6.7.6 LABORATORY EVALUATIONS

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

Complete Blood Count:

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

Serum Chemistry:

- Glucose
- Blood urea nitrogen
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase

6.7.7 PREGNANCY TESTING

For women of reproductive potential, a negative spot urine pregnancy test is required at Screening, and prior to each study treatment, HRA, DARE and surgical excision or biopsy.

6.7.8 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.

6.7.9 PARTICIPANT DIARY CARD (PDC)

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 11:59pm)
- 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 days post dose phone calls and at the next in-person visits.

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 criteria for a Grade 1 or higher AEs should be documented as an AE 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.

6.8 INJECTION AND ELECTROPORATION (EP)

Subjects will receive at least three doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by IM injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 5PSP. A fourth dose is optional for those assessed to be partial responders at the Week 36 efficacy assessment. Study treatment plus EP must not be given within 2 cm of a tattoo, keloid or hypertrophic scar, or if there is implanted metal within the same limb. EP may not be performed in the same arm adjacent to an implantable medical device (e.g., cardiac pacemaker, defibrillator or retained leads following device removal). The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, and at Week 40 (for Subgroup C only). Please refer to the Investigator's Brochure for further information.

6.9 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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, and Weeks 4 and/or Week 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.

6.10 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 into the study as listed in the Schedule of Events (Table 3).

6.11 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

The injection site will be assessed by study personnel prior to and between 30-45 minutes after each study treatment. Subjects will be advised to record local and systemic AEs for 7 days after each study treatment on a PDC which will be reviewed with study personnel 8 – 14 days after doses 1 and 2, Week 15, and 8-14 days after dose 4 (if applicable).

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any AEs, 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 AEs will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's Case Report Form (CRF).

6.12 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 6.

Table 6: 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 "Food and Drug Administration (FDA) Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" *In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

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

6.13 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, PRO instruments will be administered. The following PRO questionnaires will be used:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [25]. SF-36v2™ will be administered at the following time points:
  - Day 0 (***before*** the first study treatment)
  - 8-14 days post dose 1
  - Week 4
  - 8-14 days post dose 2
  - Weeks 12, 15, 36, 40
  - 8-14 days post dose 4* (only for those who received a 4th dose)
  - Weeks 64, 88
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [26, 27] and will be administered as described below:
  - Day 0 (***before*** the first study treatment)
  - 8-14 days post dose 1
  - Week 4
  - 8-14 days post dose 2
  - Weeks 12, 15, 36, 40
  - 8-14 days post dose 4* (only for those who received a 4th dose)
  - Weeks 64, 88

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

- **Additional Global PRO Questions-** regarding quality of life after surgery or biopsy. These two questions will be administered at Week 40 only.

6.14 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (Screening and Day 0 prior to dosing) and at Weeks 15, 36, 64 and 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding enzyme-linked immunosorbent assay (ELISA) may be performed to measure the anti–HPV-16/18 Ab response induced by VGX-3100.

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

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 and Weeks 15 and 36. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

6.15 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then the relevant paraffin blocks may be collected for the assessment of proinflammatory and immunosuppressive elements. . Assessment of markers may include, but are not limited to, CD8+ and FoxP3+ infiltrating cells as well as Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.16 HUMAN LEUKOCYTE ANTIGEN TYPING

Human Leukocyte Antigen testing will be performed on PBMC from a single blood sample collected for immunogenicity analysis if available.

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

6.17 ANAL AND/OR PERI-ANAL HPV TESTING

All intra-anal and/or peri-anal lesions of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL sites(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Intra-anal and/or peri-anal swabs will undergo HPV testing using a PCR based assay, SPF10.

The subject will be requested to abstain from sexual activity and refrain from the use of douching to eliminate potential interference with the results of HPV testing.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 in ThinPrep™ collection media. The HPV Cobas test will be performed on the ThinPrep™ specimens at Screening, and Weeks 36 and 64 when applicable. Anal cytology will be performed on intra-anal samples. At each of these visits, a recent history will be collected via self-report.

6.18 HPV TESTING FROM OTHER ANATOMICAL SITE (NON-ANAL)

Vaginal, cervical (female subjects), penile (male subjects), and OP rinse samples (all subjects) will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess virologic clearance at non-anal sites using a PCR based HPV assay, SPF10. All samples will be read in a central laboratory.

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

6.19 ANAL PHOTOGRAPHS AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of anal or anal/peri-anal HSIL confirmed by the PAC at Screening. Subjects will undergo HRA at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 to identify all intra-anal lesion(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression.

Photography of all qualifying intra-anal and/or peri-anal lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. For all peri-anal lesion(s), digital photographs will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Weeks 36, 64, and 88 compared to baseline.

If the intra-anal and/or peri-anal tissue sample(s) result suggests progression to cancer, the Investigator may schedule an ad hoc visit to perform HRA and possible biopsy if clinically indicated.

6.20 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 will discontinue further study treatment and continue in the study for safety follow-up visits. The subject will be managed according to standard of care and the Investigator's judgment based on the results of the histological diagnosis from the unscheduled biopsy. All biopsy samples/excised tissue (including standard of care) will be sent to the central pathology lab for review by the PAC.

6.21 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 the 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, nasal, topical, 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.

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.

6.22 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, including illicit drugs, taken to the Investigator and/or other study personnel. To remain in the study, illicit drugs should not be taken.

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

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

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

As a requirement for inclusion in the HPV-203 study, Investigators will only be chosen if they are experienced in the management of anal cancer, and are experienced in performing HRA.

HPV-203 Investigators are instructed to perform additional, ad hoc HRA exams and biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analyses. These additional measures should minimize the risk of progression of anal or anal/peri-anal HSIL and the risk of harboring an undiagnosed occult early invasive anal or anal/peri-anal cancer. The frequency of close monitoring by experienced Investigators should minimize the risk of cancer progression during the study and the additional measures are beyond what is expected in standard of care.

7.2 ADVERSE EVENTS (AEs)

An 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 AEs 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 IP. Adverse Events 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.

Adverse Events 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 increased 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 demise, still birth, congenital anomaly of fetus/newborn);
- AEs that occur from the study Screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE;
- Conditions that lead to a medical or surgical procedure.

Adverse Events do not include the following:

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

7.3 SERIOUS ADVERSE EVENTS

A SAE is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the

hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an Emergency room (ER) or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, or 3) the development of drug dependency or drug abuse.

Classification of Serious Adverse Events:

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

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.15.

7.4 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose; for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the AEs. An AE 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 ADR report for expectedness, to determine if it is a serious unexpected

suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of serious expected AEs, 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

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 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 and clinical AEs or SAEs with respect to the following levels of severity as per CTCAE v 4.03 for applicable patient populations:

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

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

7.7 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable causal relationship to the administration to either or both IP and/or the CELLECTRA™ 5PSP device. The Investigator will assess causal relationship of the AE separately to each of the investigational drugs and also the investigational device. The reasonable causal relationship means that there are facts (evidence) or arguments to suggest a causal relationship. An AE may also be assessed as not related to either or both IP and/or

investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs 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 AE 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 VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation or deemed clinically significant by the Investigator must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, and 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 Sections 7.2 and 7.3. 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 is assessed as detailed in Section 7.6.

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT).

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines not only the severity of the event but also whether the abnormality in question is "clinically significant (CS)" or "NCS." CTCAE v. 4.03 grading criteria can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.9 POST-TRIAL 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 probably or possibly related to the study treatment, he/she should promptly document and report the event to the Sponsor.

7.10 PROCEDURES FOR DOCUMENTING PREGNANCY DURING THE TRIAL

Subjects who are pregnant or expect to become pregnant during the course of the study will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further treatments with the IP. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax or email, as described in Section 7.15. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further 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 Screening procedure through the follow up visits must be reported. The Investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the Sponsor.

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up

period. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.11 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 88.

The sources of AEs cover:

1. The subject's response to questions about his/her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF.

Any SAE occurring during the course of the study must be reported to the Sponsor within 24 hours of awareness.

7.12 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 AEs classified by system organ class (SOC), preferred term, severity, and relationship to study treatment;
- Changes in safety laboratory parameters (e.g., hematology and serum chemistry);
- 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.

7.12.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

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

As per the Toxicity Grade for Healthy Adults, the most severe grade for that particular event is to be documented in the CRFs.

Sites will inform the Sponsor via method described in Section 7.15 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.13 ADVERSE EVENT REPORTING

To assure the safety of the participants, information about all AEs (see Section 7.2), whether volunteered by the subject, discovered by the 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.

7.14 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited AEs will be collected throughout the study and recorded in the Electronic Data Capture (EDC) system. The Study Report will analyze and summarize all AEs throughout the study. Emphasis will be placed on the following:

1. Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately
2. Unsolicited AEs will be collected and summarized for the entire study period

7.15 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS AND AESIS

The reporting period for SAEs (without regard to causality or relationship) and AESIs is comprised of the period following the signing of the ICF through Week 88. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator will complete the SAE/AESI Report form and report the event to the Sponsor within 24 hours of becoming aware of the event. The Investigator may also directly report this event to the EC according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.5 (UADE) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant 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.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the Investigator becomes aware

of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the Investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION

MEDICAL MONITOR: [redacted], M.D., Ph. D.
EMAIL: [redacted]

SAE REPORTING INFORMATION

EMAIL: safety.inovio@apcerls.com
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is an attachment to an e-mail message, to the email address as indicated above. Any SAE supporting documents provided by facsimile (Fax) are to include a coversheet that identifies the reporter name and contact information of the study site.

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.

In addition to providing the SAE report to the Sponsor or designee within 24 hours of becoming aware of the event, the AE that is serious must be recorded in the AEs eCRF. The entry into the eCRF is required to be done as soon as possible.

The Investigator will supply the Sponsor and the IRB with more information as it becomes available and any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

When recording the SAE form, correct medical terminology/concepts are to be used and the use of abbreviations and colloquialisms are to be avoided.

Serious Adverse Events 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.

In the event of a pregnancy, the Investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

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 experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.4 and 7.16).

7.17 REPORTING OF CELLECTRA™5PSP DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported within 24 hours of becoming aware of the event per Sections 7.2 and 7.3.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form provided must be completed and emailed to the Sponsor at clinicalcomplaint@inovio.com.

Additional instructions on complaint reporting to be provided separately.

7.18 TRIAL DISCONTINUATION

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

Should the trial be terminated and/or the site closed for any reason, all investigational drugs & devices must be returned to INOVIO or its representative. The PI should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 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 or its representative.

This is a single-arm, multi-center, open-label clinical trial of VGX-3100 in subjects with a diagnosis of AIN2, AIN3, PAIN2, or PAIN3 associated with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of AIN/PAIN HSIL and viral clearance of HPV-16/18 based on tissue collected at Week 36. The primary hypothesis is that the treatment will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16/18 infection, complete regression, non-progression, and anatomic extent. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory efficacy analyses concern extended dosing with respect to regression, clearance, clearance among non-anal anatomic locations, and effect of HLA type on efficacy and association of miRNA profile, anoscopy, cytology, and virology with efficacy. Other exploratory analyses pertain to tissue immunological measures and PRO.

8.3 STATISTICAL HYPOTHESES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations are:

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.05 and the corresponding lower bound of the one-sided 95% CI exceeds 0.15.

For the analysis, the efficacy time frame is defined by any time starting from 14 days prior to the -specified visit week.

8.5.2 SECONDARY ANALYSES

The secondary efficacy binary 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.

The anatomic extent endpoint will be analyzed by calculating the mean percent change in surface area and the mean percent change in number of lesions and associated 95% t-distribution based confidence intervals.

Post-baseline ELISA titers will be summarized with geometric mean and associated 95% CIs. Post-baseline increases in ELISPOT and Flow responses will be summarized with tobit-based means and 95% CIs. Valid samples for statistical analysis purposes will be those collected within 14 days of the specified visits. Baseline is defined as the last measurement prior to the first treatment administration.

8.5.3 SAFETY ANALYSES

All AEs will be summarized among the safety population by frequency. These frequencies will be presented overall and separately by dose, and will depict overall, by SOC 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 AE data will be based on events occurring within 28 days following any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days following any dose and regardless of when they occurred.

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

8.5.4 DISPOSITION

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

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables for the mITT population.

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

Prior medications are those that were used and stopped 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. Data for all prior medications will be summarized with percentages for the mITT population.

8.5.6 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 will not be adjusted for possible early stopping due to futility.

8.5.7 MULTIPLICITY

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

8.5.8 MISSING VALUES

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.

No other missing data will be imputed or replaced.

8.5.9 EXPLORATORY ANALYSES

The exploratory efficacy binary 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.

Other analyses will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) HRA results, d) cytology results, and e) HPV results. Relationships will be examined with contingency tables and/or logistic regression models which model the primary endpoint versus these results as regressor variables.

The change in tissue immune response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.6 SAMPLE SIZE/POWER

A sample of 24 subjects provides ~80% power to declare superiority over historical control, assuming the true proportion of subjects who achieve the primary endpoint is 40% for the treatment arm versus 15% for the historical control, and that 90% are evaluable at Week 36 from 1st dose.

8.7 RANDOMIZATION AND BLINDING

This is an open-label trial, and therefore, site personnel, individual subjects and INOVIO or its representative trial personnel will be aware of the treatment allocations for this trial. Randomization does not apply.

9.0 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical trial 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

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., ICF, 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:

- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of trial-related information (refer to trial files) that include all correspondence with the IRB/EC.
- Notify the IRB/EC when the trial is completed (i.e. after the last visit of the final trial subject).
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.

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 OFFICE OF BIOTECHNOLOGY ACTIVITIES

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 [NIH] Office of Biotechnology Activities [OBA]) governing research that involves recombinant or synthetic nucleic acid.

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 trial, 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 (Section 6.1).

9.5.2 COMPLIANCE WITH IRB/EC REQUIREMENTS

This trial 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 trial 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.

9.5.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURE REGULATIONS (21CRF PART 11)

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

9.5.5 COMPLIANCE WITH PROTOCOL

Subjects will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviation (PD), should a deviation be discovered, Sponsor must be informed immediately. Any PD 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 prior review and documented approval/favorable opinion from the Sponsor and IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects. While every effort should be made to avoid PD, should a

deviation be discovered, Sponsor must be informed immediately. Any PD impacting Subject safety must be reported to the Medical Monitor immediately.

10.0 DATA COLLECTION, MONITORING, AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial 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 trial Sponsor, the governing health authorities or the FDA, if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

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

Information about trial subjects will be kept confidential and managed in accordance with the requirements of the HIPAA of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

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

11.0 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 trial.

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.

Case Report Form will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified with an SID.

It is the Investigator's responsibility to retain trial essential documents for at least two (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 two (2) years have elapsed since the formal discontinuation of clinical development of the IP. 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.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY AND QUALITY MONITORING

An independent 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 there appears to be a regression with VGX-3100.However, no formal interim analysis will be performed.

12.2 PATHOLOGY ADJUDICATION COMMITTEE

All anal biopsies will be read by a central expert PAC to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion. The logistics and details of the PAC are detailed in the PAC Charter.

12.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:

- Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
- Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities continue to be acceptable.
- Compare the trial 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.

13.0 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 at least 60 days prior to submission for publication. The Sponsor will have 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) will 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 US Patent and Trademark Office and/or foreign patent office(s).

14.0 LIST OF ABBREVIATIONS

Ab	Antibody
ADR	Adverse Drug Reaction
AEs	Adverse events
AESI	Adverse Event of Special Interest
AIN	Anal Intraepithelial Neoplasia
AIS	Adenocarcinoma-in-situ
ALT	Alanine Aminotransferase
BMI	Body Mass Index
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIN	Cervical Intraepithelial Neoplasia
CIN1	Grade 1 Cervical Intraepithelial Neoplasia
CIOMS-I	Council for International Organizations of Medical Sciences
Cr	Creatinine
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CPK	Creatine Phosphokinase
DARE	Digital Anal Rectal Examination
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
ELIspot	Enzyme-linked Immunospot Assay
EP	Electroporation with CELLECTRA™5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ER	Emergency Room
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
gbm	gay and bisexual men
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HRA	High-resolution Anoscopy
HR-HPV	High-risk HPV Type
HSIL	High Grade Squamous Intraepithelial Lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug

INOVIO	Inovio Pharmaceuticals, Inc.
IP	Investigational Product
IRB	Institutional Review Board
IRB/IEC	Institutional Review Board or Independent Ethics Committee
ISO	International Organization for Standardization
LAST	Lower Anogenital Squamous Terminology
LSIL	Low Grade Squamous Intraepithelial Lesion
miRNA	MicroRNA
mITT	Modified Intent to Treat
MSM	men who have sex with men
NCS	Not Clinically Significant
OBA	Office of Biotechnology Activities
OP	Ororpharyngeal
PAIN	Peri-anal Intraepithelial Neoplasia
PAM	Protocol Administrative Memo or Letter
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIN	Penile Intraepithelial Neoplasia
PP	Per Protocol
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PE	Physical Exam
PRO	Patient-reported Outcome
SAEs	Serious Adverse Events
SF-36v2™	36-Item Short Form Health Survey
SID	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPANC	Study of the Prevention of Anal Cancer
SSC	Saline Sodium Citrate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumor Necrosis Factor
UADE	Unanticipated (Serious) Adverse Device Effect
US	United States
VAIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
WFI	Water for Injection
WOCBP	Women of Childbearing Potential

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16.0 APPENDICES

HPV-203

A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal, High grade squamous intraepithelial lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 13683

Protocol Version: 2.0
Protocol Version Date: 15May2019

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.1 dated 08 November 2017 to Version 2.0 dated 14 May 2019. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Effective 05Jul2018, the Medical Monitor for HPV-203 is [redacted]. This has been previously addressed in PAM #3 (25Jan2019) and is now incorporated into this amendment. [redacted] contact information is as follows:
   [redacted], M.D., Ph.D.
   Phone: [redacted]
   Email: [redacted]
2. We have added clarifying language to the primary endpoint to indicate our endpoint will be assessed based on qualifying lesions which is defined in the applicable footnote.
3. The language from Protocol Version 1.1 indicates: For all peri-anal lesion(s), digital photos will be analyzed with a computer program to assess the percent reduction in the cumulative surface area of the peri-anal lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Weeks 36, 64, and 88 compared to baseline. We will no longer be using a computer program to determine the percent reduction in cumulative surface area. Therefore the new language is as follows: All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64 and 88. The applicable objective (secondary objective #7), corresponding endpoint remains unchanged. This was previously clarified in PAM #1 (11May2018) and is now incorporated into this amendment.
4. We have included instructions based on the outcome of the Week 64 biopsy results. If HSIL remains, the subject will receive standard of care treatment and remain on the study for follow up and safety only.
5. HLA typing will no longer be done for this study. HLA typing has been removed throughout this protocol as well as the informed consent form (ICF).
6. Exclusion criteria #1 (Protocol Version 1.1, 08Nov2017) states that subjects will be excluded from the study if they have 'untreated micro invasive cancer'. This criterion was previously clarified in PAM #3 (25Jan2019) and includes subjects who have microscopic or gross evidence of invasive cancer, or the suspicion of cancer in any histopathologic specimen by any pathologist at screening.
7. For exclusion criteria numbers 2, 3, 4, and 5 (Protocol Version 1.1, 08Nov2017) a superscript has been added to clarify that if the standard of care is observation then this will not exclude a subject from participating.
8. Inclusion criteria #3 which was previously clarified in PAM #3 (29Jan2019) allows for an HIV rapid test to be performed as long as the following is adhered to: 1. The test is an antigen/antibody immunoassay, 2. The test is only done using blood, 3. The test must be performed in the office and done by qualified study staff members.

9. Exclusion Criteria #11 in Protocol Version 1.1, 08Nov2017 indicates that subjects with 'the presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator,' will be excluded from the protocol. This criterion was intended to exclude subjects with unresolved lab abnormalities. If the lab is redrawn and the result from the redrawn sample no longer meets Exclusion Criterion #11, then the subject should no longer be excluded on the basis of this criterion. This has previously been clarified in PAM #1 (18May2018) and is now incorporated into this amendment.
10. Exclusion Criteria #14 in Protocol Version 1.1 reads: 'Receipt of any non-study related non-live vaccine within 2 weeks of any VGX-3100 dose.' The two week period applies to both before and after having received any VGX-3100 dose and therefore will now read: 'Receipt of any non-study related non-live vaccine within 2 weeks before or after having received any VGX-3100 dose.' This will ensure subjects do not receive non-live vaccines after being dosed with VGX-3100 for 2 weeks. This has been previously clarified in PAM #5 (25Feb2019) and is now incorporated into this amendment.
11. Exclusion Criteria #15 in Protocol Version 1.1 reads: 'Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of any VGX-3100 dose.' The 4 week period applies to both before and after having received any VGX-3100 dose: 'Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks before or after having received any VGX-3100 dose. This will ensure subjects do not receive live vaccines after being dosed with VGX-3100 for 4 weeks. This has been previously clarified in PAM #3 (25Jan2019) and is now incorporated into this amendment.
12. Clarification of HRA at Screening: Protocol Version 1.1 allows for historical biopsy samples (i.e. blocks) to be sent to the study lab within the allowable window of 10 weeks from the date of collection until the date of first study treatment (Day 0). Since HRA must be performed in order to obtain the biopsies; if a historical biopsy is used with a corresponding historic HRA evaluation, then the HRA does not need to be repeated for Screening to determine eligibility as long as it is within the allowable window of 10 weeks. This has been previously clarified in PAM #4 (19Feb2019) and is now incorporated into this amendment.
13. Section 6.20 Unscheduled Biopsies: Protocol Version 1.1 states: 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 will discontinue further study treatment and continue in the study for safety follow-up visits. This is inconsistent from the definition of responder and non-responder for primary endpoint in Table 2 where one of the criteria of non-responder is any non-study treatment of curative intent of intra-anal and/or peri-anal lesions. We have changed this section to state: 'Unscheduled biopsies may be performed on new lesions or suspected progression of original lesions per the Investigator's medical judgment during the study. 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. All biopsy samples/excised tissue (including standard of care) will be sent to the central pathology lab for review by the PAC.'

14. Section 6.3.3: Patient Report Outcomes at the Week 4 Visit was previously clarified in PAM #2 (19Jul2018) to indicate that the PROs will be completed after study treatment at the Week 4 visit and after the Week 12 visit and are now incorporated into this amendment.
15. Section 6.3.9 Patient Reported Outcomes at the Week 40 visit was previously clarified in PAM #2 (18Jul2018) to indicate that a subject must complete the SF-36v2, the EQ-5D-5L and the two additional 'global' questions at the Week 40 visit; this has been incorporated into this amendment.
16. Section 6.3.12 previously clarified in PAM #2 (18Jul2018) states that a full physical examination will occur at the Week 88 visit and is now incorporated into this amendment.
17. The last paragraph of Section 8.5.3 Safety Analyses has been removed because safety labs are only performed at the screening visit, and therefore changes between the baseline and other time points are not applicable. This was previously addressed in PAM #3 (25Jan2019) and will now be incorporated into this amendment.

Medical Monitor Approval Page

Drug: VGX-3100

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

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

Approval Signature:

[redacted] M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals

[redacted]
Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board/Ethics committee approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 (IRB/IEC) 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 International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

<Insert Principal Investigator Printed Name>	Date (dd/Mmm/yyyy)

Site Number: _____

Site Name: _____

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal High-Grade Squamous Intraepithelial Lesions, HSIL (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2
Protocol Number: HPV-203
Trial Phase: 2a
Estimated Number of Trial Centers and Countries/Regions: Approximately 3 study centers located in North America
Formulation: VGX-3100
Trial Design: Multi-center, single-arm, open-label phase 2 study
Criteria for Evaluation: To provide a treatment to regress anal or anal/peri-anal HSIL and clear the related HPV-16 and/or HPV-18 (HPV16/18) in individuals that are seronegative for HIV-1/2. **Research Hypothesis:** VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal HSIL[1], (AIN2[2], AIN3[3], PAIN2[4], PAIN3[5]) associated with HPV-16 and/or HPV-18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.
Dose of VGX-3100: 6 mg (1mL)
Administration: Intramuscular injection followed by EP
VGX-3100 Dosing Schedule: Day 0, Week 4 and Week 12 with one additional dose given to partial responders at Week 40
Study Duration: 88 Weeks
Primary Objective: Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18.
Primary Endpoint: Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL[6] on histology (i.e., collected via biopsy or excisional treatment)[7] and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue qualifying lesions[8].

[1] High-grade Squamous Intraepithelial Lesion
[2] Grade 2 Anal Intraepithelial Neoplasia
[3] Grade 3 Anal Intraepithelial Neoplasia
[4] Grade 2 Peri-anal Intraepithelial Neoplasia
[5] Grade 3 Peri-anal Intraepithelial Neoplasia
[6] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.
[7] A treatment responder is defined as a subject with no histologic evidence of anal or anal/peri-anal HSIL and no evidence of HPV-16 or HPV-18 in anal lesion tissue and who did not receive any non-study treatment of curative intent of intra-anal and/or peri-anal lesions. A treatment non-responder is defined as a subject with histologic evidence of anal or anal/peri-anal HSIL, adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma or a subject with evidence of HPV-16/18 in anal lesion tissue or a subject who received non-study treatment of curative intent of intra-anal and/or peri-anal lesions.

[8] An intra-anal and/or peri-anal lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed anal or anal/peri-anal HSIL by the Pathology Adjudication Committee (PAC).

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC). 1b. **All** adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study (through the Week 88 visit)
2. Determine the **efficacy** of three doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL[9] on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
3. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue	3. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18[10] from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
4. Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal tissue swab testing	4. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
5. Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue	5. Proportion of subjects with **no evidence** of anal or anal/peri-anal Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
6. Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL	6. Proportion of subjects with **no progression**[11] of anal or anal/peri-anal HSIL to carcinoma from baseline[12] to histology (i.e. biopsies or excisional treatment) at the Week 36 visit
7. Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in size of peri-anal lesion(s) if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36	7. Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s), and the reduction in size of peri-anal lesion(s) as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline[12].

8. Determine the humoral and cellular immune response following dose 3 and additional time points compared to baseline	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline and the Weeks 15, 36, 64, and 88 visits 8b. Interferon-γ ELISpot response spot forming units (SFU) at baseline and the Weeks 15, 36, 64, and 88 visits 8c. Flow Cytometry response magnitude at baseline and Week 15 visit

[9] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.

[10] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.

[11] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.

[12] Baseline photographic imaging is defined as photographs obtained pre-biopsy at Screening, or post biopsy at Screening (for subjects with historical biopsy tissue).

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16 and/or HPV-18	1. Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
2. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
3. Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18	3. Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
4. Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples	4. Assessment of proinflammatory and immunosuppressive elements in tissue, where feasibile[13]
5. Describe the **clearance** of HPV-16 and/or HPV-18 infection from non-anal anatomic locations	5. Proportion of subjects who have **cleared** HPV-16 and/or HPV-18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
6. Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression	6. HRA, cytology, and HPV test results and miRNA profile (baseline and at the Weeks 15 and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit
7. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100	7. Patient reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose

[13]Additonal assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possible other relevant markers identified in the literature as sample allows.

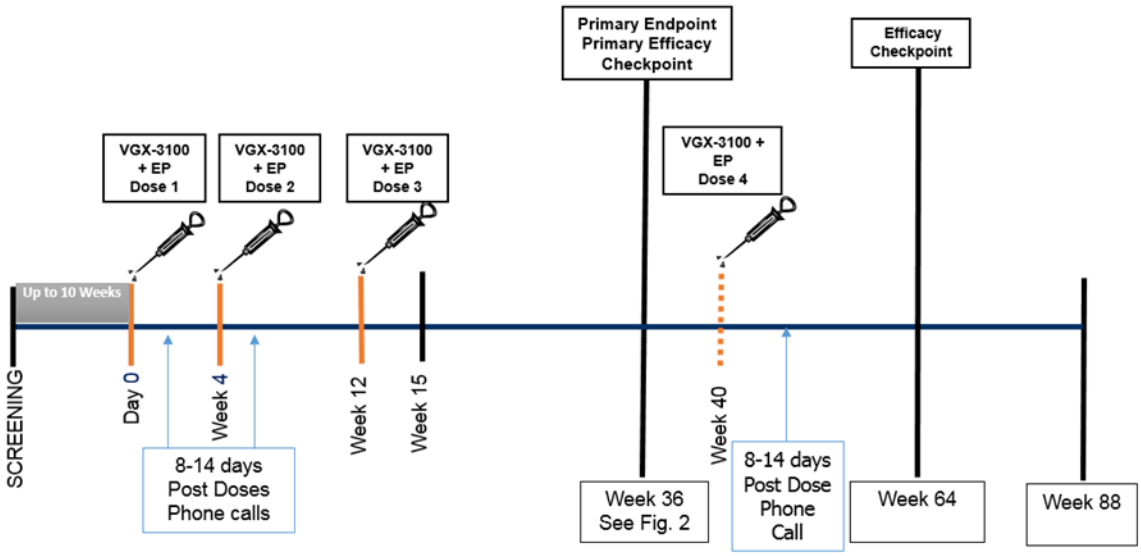
Study Design:

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or HPV-18.

Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40.

All subjects are scheduled to be followed to Week 88.

Figure 1: HPV-203 Study Visit Schedule



Biopsy (ies) will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Subjects must also have intra-anal and/or peri-anal lesion(s) tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

Visualization of the lesion and digital anal rectal examination (DARE) alone are insufficient evidence to confirm disease regression. Disease regression will be primarily based on histopathologic assessment at Week 36 and additionally assessed at Week 64. Subjects will be monitored during the course of the study by DARE and HRA. Intra-anal lesion(s) will be assessed at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 using HRA. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

The decision process following the results of the Week 36 biopsy are described below in ***Figure 2*** and are as follows: At Week 36, the subject will undergo repeat intra-anal and/or peri-anal punch biopsies of all HSIL lesions confirmed by the PAC at Screening of adequate size (≥ 4mm). (See

Table 1 for Minimally Required Biopsy Procedures). If after evaluation of the biopsy tissue(s) by the PAC there is no evidence of HSIL (defined by Subgroups A or B), the subject will continue to Week 64 for HRA and undergo biopsies of the same areas (HSIL lesions) as the baseline biopsies. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only.

Figure 2: Decision process at Week 40

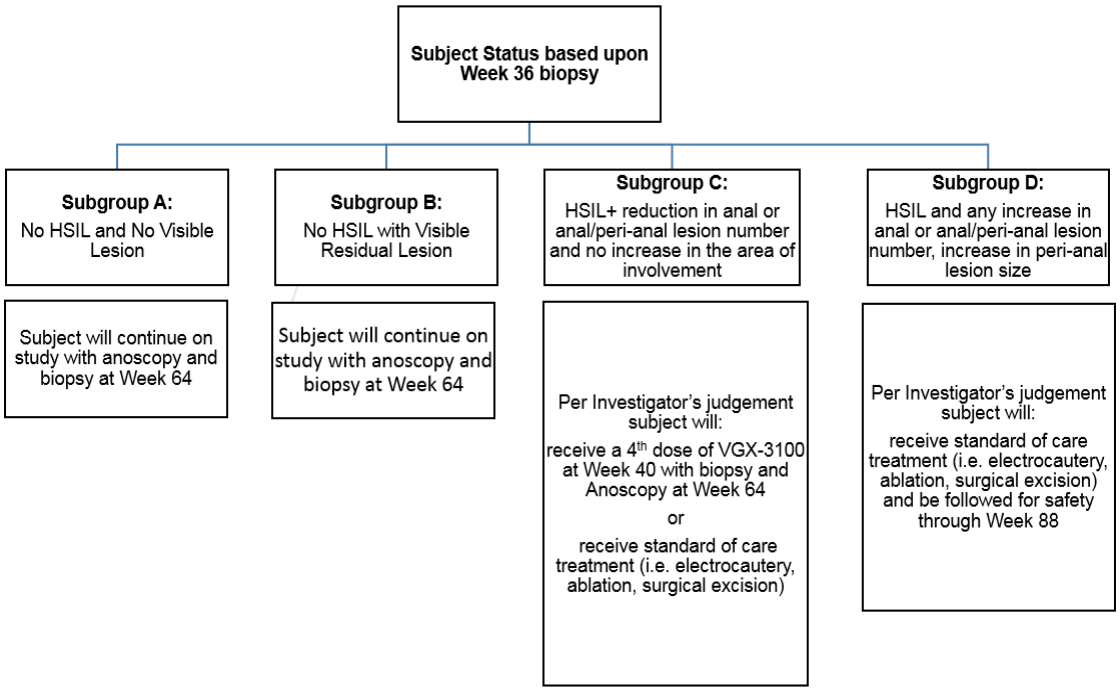


Table 1: Minimally Required Procedure at each Biopsy Visit

Pre-biopsy High Resolution Anoscopy Finding	Minimally required procedure
No lesion	Punch biopsy and photography; biopsy should be collected from within the approximate original boundaries of the study entry HSIL as proximal as possible to the original biopsy site which was previously determined to be HSIL by the PAC.
Single lesion (which was also present at baseline)	Punch biopsy and photography; biopsy should be collected within the boundaries of the original lesion and from the area most suspicious for advanced disease within the lesion by clinical exam.
Multiple lesions	Punch biopsies and photography; biopsy should be collected from the same lesions diagnosed as HSIL from study entry and from the area most suspicious for advanced disease within the lesion by clinical exam.

If HSIL is diagnosed in any Week 36 biopsy, but there is a reduction in the number of intra-anal and/or peri-anal lesion(s), reduction in peri-anal lesion(s) size or no change in peri-anal lesion(s) size from baseline (defined by Subgroup C), the Investigator has the option to administer a 4th dose of VGX-3100 at Week 40, and the subject will continue on the study to have HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may instead choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of standard of care.

In the event of worsening anal or anal/peri-anal HSIL at any time during the trial (defined as any increase in lesion(s) area from baseline or worsening of anal or anal/peri-anal HSIL to cancer), the subject may receive standard of care treatment (i.e. electrocautery, ablation, surgical excision) per the Investigator's judgment but will continue on the study through Week 88 with HRA, but without further biopsy unless it is part of the standard of care.

If there is histologic progression to carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment but will continue through Week 88 with HRA, but without further biopsy unless it is part of the standard of care. The event will be reported as an SAE per Section 7.3. If wide excision is required, the sample(s) obtained will be sent to the PAC for evaluation.

Efficacy Assessment:

Screening biopsies will be collected from all intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm). Visible lesion(s) observed during HRA should be large enough to biopsy, but

the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and/or HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal tissue, utilizing HRA with biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Tissue samples will be analyzed for evidence of histopathologic regression. Clearance of HPV-16 and/or HPV-18 will be determined using the type specific HPV PCR test on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be collected at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) rinse samples will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only.

Immunogenicity Assessment: Humoral and cell mediated immune responses to VGX-3100 may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, 64, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

Virologic Assessment: Intra-anal and/or peri-anal swabs will be obtained to characterize HPV infection at Screening, Day 0, and Weeks 4, 15, 28, 36, 64 and 88. Likewise, PCR-based assessment of histological samples will occur at Screening and Weeks 36 and 64.

For testing of non-anal sites, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) samples (all subjects) will be obtained to characterize HPV infection at Day 0, and at Weeks 4,15, 28, 36, 64 and 88.

Safety Assessment: Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the Participant Diary Card (PCD).

2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed to Week 88.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. Refer to Section 3.8 for stopping rule criteria.

Definition of Responder and Non-Responder for Primary Endpoint:

Responder and non-responder definitions (
Table 2) take into account both histopathologic regression of anal or anal/peri-anal HSIL and virologic (HPV-16/18) clearance as measured by intra-anal and/or peri-anal tissue since HPV persistence is an important factor in the clinical progression of HSIL. Any case of histologically confirmed progression from HPV-16/18 positive anal or anal/peri-anal HSIL to carcinoma is considered a non-responder.

Table 2: Definition of Responder and Non-Responder for Primary Endpoint

Responder	Non-Responder
No histologic evidence of anal or anal/peri-anal HSIL AND Negative PCR for HPV-16 or HPV-18 in anal lesion tissue AND No non-study treatment of curative intent of intra-anal and/or peri-anal lesions	Histologic evidence of anal or anal/peri-anal HSIL, anal Adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma OR PCR positive for HPV-16 or HPV-18 in anal lesion tissue OR Any non-study treatment of curative intent of intra-anal and/or peri-anal lesions

Study Population:
Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2[a] within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16 and/or HPV-18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue (blocks only) provided to the Study Pathology Adjudication Committee (PAC) for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    a. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    a. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40mIU/mL;
    b. Surgically sterile due to absence of ovaries or due to bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    c. Subject agreement to avoid pregnancy for one month after last dose (Week 12 or Week 40);
    d. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of investigational product (Week 12 or Week 40). The following are acceptable methods:
        i. Hormonal contraception: either combined progestin-alone including oral contraceptive, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g. deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;
9. Men who would father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

[a] An HIV rapid test may be used given the following conditions are met: 1. The test is an antigen/antibody immunoassay, 2. The test is only done using blood, 3. The test must be performed in the office and done by qualified study staff members

Exclusion:

1. Untreated micro invasive cancer[a];
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN[b];
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN[b];
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN[b];
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN[b];
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator[c];
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    c. Long-term use (≥7 days) or oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, otic, nasal, topical, 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. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed <u>prophylactic</u> HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks before or after any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks before or after any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
17. 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 the study results (e.g. chronic renal failure, angina, myocardial ischemia or infarctation, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

[a] This criterion includes subjects who have microscopic or gross evidence of invasive cancer, or the suspicion of cancer in any histopathologic specimen by any pathologist at screening.
[b] When observation is the standard of care this will not exclude a subject from the study.
[c] If the lab is redrawn and the result from the redrawn sample no longer meets this exclusion criteria, then the subject is not excluded on the basis of this criterion

18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of Day 0;
20. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
21. 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;
22. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent form (participating in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrillator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or evaluation of any study product;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military personnel;
    d. Study-related staff or family members of study-related staff

TRIAL SCHEDULE OF EVENTS

Table 3: Schedule of Events

Study Action	Screen (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Informed consent	X												
Medical History/Demographics	X												
Medications (prior/concomitant)	X	X		X		X	X	X	X	X		X	X
Socio-behavioral assessment	X								X			X[n]	X
Inclusion/Exclusion criteria[1]	X	X											
Physical exam (PE)/assessment [a]	X	X		X		X	X	X	X	X		X	X
Vital signs	X[b]	X		X		X	X	X	X	X		X	X
Screening safety (12 lead ECG, laboratories) [c]	X												
Pregnancy Testing [d]	X	X		X		X	X	X	X	X		X	X
HIV Ab by ELISA	X								X				
Blood immunologic samples	X[e]	X[e]					X[f]		X[e]			X[e]	X[e]
Oropharyngeal (OP) rinse		X		X			X	X	X			X	X
Vaginal, cervical, and penile swab		X		X			X	X	X			X	X
Intra-anal and/or peri-anal swab	X	X		X			X	X	X			X	X
Digital Anal Rectal Examination DARE [g]	X	X		X			X	X	X			X	X
High Resolution Anoscopy (HRA) [h]	X	X		X			X	X	X			X	X
Lesion photography [i]	X	X		X			X	X	X			X	X
Biopsy [j]	X								X			X	
Inject VGX-3100 +EP[k]		X		X		X				X[k]			
Post treatment reaction assessment		X		X		X				X			
Distribute Participant Diary Card (PDC)		X		X		X				X			
Review PDC [l]			X		X		X				X	X	
Patient Reported Outcomes (PROs) (SF-36v2™) (EQ-5D-5L) [m]		X[o]	X	X	X	X	X		X	X	X[p]	X	X

[1] Subject eligibility will be reconfirmed at every visit.

[a] Full Physical exam (PE) mandatory at Screening and study discharge (Week 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE.

[b] Screening vital signs must include a measured height and weight and calculated body mass index (BMI) (Bodyweight in kilograms divided by height in meters squared). Weight will be collected at all dosing visits.

[c] Screening 12-lead Electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, alanine aminotransferase (ALT), and Creatine Phosphokinase (CPK) performed within 45 days prior to first dose administration.

[d] Negative spot urine pregnancy test is required for female subjects at Screening, prior to each study treatment, high-resolution anoscopy (HRA), and biopsy/surgical excision; the pregnancy test at Week 40 would only be needed for subjects who receive an additional dose.

[e] At least 34 mL (4 x 8.5 mL yellow (ACD) tubes) whole blood and 4 mL serum per time point. At least 68 mL whole blood and 8 mL serum should be collected prior to first dose.

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

[g] Digital Anal Rectal Examinations (DARE) are to be performed once cytology has been collected and prior to HRA.

[h] An additional visit may be scheduled to perform HRA if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening) and Weeks 36 and 64 for Subgroup C unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the Pathology Adjudication Committee (PAC) for review.

[i] Photography of qualifying lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

[j] Tissue specimen (paraffin blocks) from all excised tissue lesion(s) that led to eligibility at study entry must be reviewed by the PAC and residual tissue from entry and Weeks 36 and 64 specimen(s) (paraffin blocks) must be sent to the central laboratory for immune analysis and Human Papillomavirus (HPV) testing.

[k] Potential dosing at Week 40 is applicable for partial responders only.

[l] A phone call will be used to review the Participant Diary Card (PDC) with subject within 8-14 days following doses 1 and 2. The subject will be expected to bring the PDC to the next visits for review. Subjects who receive an additional 4th dose will also have a phone call 8-14 days post dose 4 where the PDC will be reviewed. The subject should bring the PDC to the next visit.

[m] Patient-reported outcome (PRO) measures (SF-36v2™ and the EQ-5D-5L), plus two additional "global" questions will be assessed as described in Section 6.13.

[n] This socio-behavioral assessment will only apply to those subjects in Subgroup C who receive a 4th dose of investigational product.

[o] PROs at this time point must be administered prior to first dose of study drug.

[p] PROs at this time point will only be for subjects who received a 4th dose of study drug.

1.0 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. Human Papillomavirus 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). In the United States (US), approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type (HR-HPV) and thus can cause cancer [2]. In U.S. adults through age 59 years, about 25% of men and 20% of women have genital HR-HPV infection [3]. Human Papillomavirus causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV Deoxyribonucleic Acid (DNA) was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (OP), 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS) [4]. An average of over 30,000 cases per year of HPV-attributable cancer were diagnosed during the period 2008 through 2012 in the U.S. [5]. Human Papillomavirus-16 and HPV-18 are the most significant among high-risk types since they are responsible for most HPV-caused cancers [4].

With regard to anal cancer, about 95% of cases are caused by HPV, and most of those cases are caused by HPV-16 [6, 7]; with some by HPV-18 and perhaps other HPV genotypes [2]. An estimated 8,200 new cases of anal cancer in the US are diagnosed each year (for year 2017), with an estimated 1,100 deaths annually due to this cancer [8]. In Canada, the latest available data is for year 2013, during which 580 new cases of anal cancer were diagnosed and 144 persons died due to anal cancer [9].

The precursor lesion to HPV-associated anal cancer historically was known as anal high-grade dysplasia or intraepithelial neoplasia. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term HSIL to encompass high grade dysplasia [10]. Among HPV-associated anal HSIL cases in the US, about 55% to 80% are associated with HPV-16/18, and worldwide about 80% of cases are associated with HPV-16/18 [7, 11, 12].

Left untreated, anal HSIL may progress to cancer. Spontaneous regression of these lesions may occur, but the available data indicate that such regression is in the minority of cases. For example, published results of a small observational study of anal HSIL in men who have sex with men (MSM) in Australia found spontaneous regression occurred in 29% of those HIV-negative after more than one year of follow-up time, with an even lower regression rate in those who were HIV-positive. That study also found that the majority (71%) of patients who regressed only did so to anal low-grade SIL (Low grade squamous intraepithelial lesion [LSIL]), with the remainder to normal tissue [13]. In an ongoing larger observational study of gay and bisexual men – the Study of the Prevention of Anal Cancer (SPANC) [14] -- also comprised of patients HIV-negative and HIV-positive (though with medically well-controlled CD4 cell counts), preliminary published data show that 55% of patients with anal HSIL, regardless of HIV status, had their HSIL persist to at least 12 months and HPV-16 was significantly associated with persistence as compared to other HPV genotypes (Relative Risk of 1.5) [15].

Spontaneous regression data from that study are not yet published, but preliminary data show spontaneous regression of only about 20% by one year of follow-up. Further, many of those patients who regressed later recurred to HSIL, suggesting that HSIL in some cases may be merely regressing to a level below the detection limit but is still present [16]. Other published data from a sub-study of that larger study indicate that HPV-16 E6-specific T-cell responses may be associated with recent anal HSIL regression (Pexact = 0.065) [17]. That finding provides further plausibility, in addition to other data summarized later in this protocol, that VGX-3100 plus electroporation treatment could cause anal HSIL regression.

Anal HPV infection spontaneous clearance in non-immunocompromised adults can occur, but such data are generally unavailable for persons who have anal HSIL. Nevertheless, high-risk HPV (HR-HPV) clearance by one year ranges from 56% to 78%, varying by gender and sexual preference etc., as found in large, prospective studies [18-20] with some wider variation in clearance rates for HPV-16 and HPV-18 specifically in those studies.

Collectively, the aforementioned anal HSIL regression and HPV clearance data comprise in part the historical control data that the results of the present trial will be compared to.

1.1.1 VGX-3100

VGX-3100 contains plasmids that target HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated Investigational Product (IP) designed as a non-surgical treatment of HPV-16/18-related anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, and PAIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was Water for Injection (WFI) with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This frozen formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100 was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This non-frozen formulation of VGX-3100 was administered to 117 subjects in a Phase 1 clinical trial, HPV-101 in which subjects were randomized 1:1 to receive the non-frozen or frozen formulation of VGX-3100. In study HPV-101, healthy adults received three 6 mg IM doses of VGX-3100 in the frozen or non-frozen formulations followed by EP with the CELLECTRA™ 5Pdevice. The non-frozen formulation was found 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 enzyme-linked immunospot (ELIspot) assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (frozen formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16/18 [1]. The Phase 2b study, HPV-003, enrolled 169 subjects with high grade cervical dysplasia from seven countries and one US Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, US and Puerto Rico). Subjects were randomized in a 3:1 ratio to treatment with VGX-3100 or placebo, respectively. All

subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or Loop Electrical Excision Procedure (LEEP) of the cervix at Week 36 to assess efficacy defined as regression of high grade Cervical Intraepithelial Neoplasia (CIN) by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to Grade 1 Cervical Intraepithelial Neoplasia (CIN1) or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol (PP) and modified Intent to Treat (mITT) analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.2 ELECTROPORATION

CELLECTRA® 2000 & CELLECTRA™ 5PSP are both electroporation (EP) devices developed by INOVIO. Electroporation with CELLECTRA™5PSP 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 [21, 22]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced immunogenicity by 10 to 100 fold [23, 24]. 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 [21]. 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) [22, 23].

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 U.S. 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-16/18 related 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.

Inovio Pharmaceuticals Inc. device experience demonstrates that delivery of its proprietary electroporation pulses into muscle immediately following injection of DNA plasmids (including VGX-3100) is well-tolerated in humans and no significant safety issues have been identified [1, 22, 24]. For further information concerning the CELLECTRA™ 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.3 DOSE RATIONALE

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

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 (AEs) from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in HPV-003, Phase 2b study. The results obtained in the phase 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 2 trial [1].

1.2 POTENTIAL BENEFITS

Currently accepted surgical treatments are associated with a high recurrence rate, >50%. The current surgical approaches also have risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the anus. This study has been designed to provide non-surgical treatment with an aim of regression of the anal or anal/peri-anal HSIL and thus avoiding the need for surgical excision, infrared coagulation, electrocautery and laser therapy. In the absence of complete resolution of intra-anal and/or peri-anal lesions, there would still be potential benefit from a partial response, which would reduce or minimize the need for excisional or ablative treatment modalities. The other potential benefit is that the response to VGX-3100 is systemic and may clear the underlying HPV infection, which is the root cause. Consequently, there is the potential to reduce the risk of recurrence of anal or anal/peri-anal HSIL.

1.3 POTENTIAL RISKS

Risks associated with VGX-3100 for the treatment of anal or anal/peri-anal HSIL are injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience with VGX-3100 with healthy volunteers and in women with cervical HSIL, 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 anal dysplasia and possible missed diagnosis of an occult early invasive cancer for the VGX-3100 non-responders, who do not spontaneously regress. Although professional guidelines typically advocate excisional therapy for adults with HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [10]. The risk of a missed diagnosis of an occult early invasive cancer exists for all current treatment modalities including surgical and ablative therapies. To mitigate these potential risks the study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult

early invasive cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent High-resolution anoscopy (HRA) and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced physicians, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

An independent Data and Safety Monitoring Board (DSMB) will also advise the Sponsor if it appears that the frequency of regression is unacceptably low. These measures should minimize the risk of progression of the HSIL and the risk of harboring an undiagnosed occult early invasive cancer.

In the HPV-003 study of women with cervical HSIL, 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 and even lower than the 6.7% that has been reported under standard of care settings [18].

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

2.0 PURPOSE AND HYPOTHESIS

2.1 PURPOSE

To provide a treatment to potentially regress and clear HPV-16/18 related anal or anal/peri-anal HSIL in individuals that are seronegative for HIV-1/2.

2.2 HYPOTHESIS

VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal high-grade squamous intraepithelial lesions, HSIL, (AIN2, AIN3, PAIN2, PAIN3) associated with HPV-16/18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.

3.0 TRIAL DESIGN AND ENDPOINTS

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or 18. Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40. All subjects are scheduled to be followed to Week 88.

To be eligible for the study, subjects must consent to participate and agree to the collection of anal lesion tissue samples for anal cytology and genotyping, a Digital Anal Rectal Examination (DARE), blood samples for immunologic) assessments, HRA and

HRA guided biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening.

Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Subjects must also have intra-anal and/or peri-anal lesion tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

3.1 PRIMARY OBJECTIVE(S)

Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16/18

3.2 PRIMARY ENDPOINT(S)

Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL on histology (i.e., collected via biopsy or excisional treatment) and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue for qualifying lesions

3.3 SECONDARY OBJECTIVE(S)

- Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by testing from lesion tissue
- Determine the **efficacy** of VGX-3100 as measured by **virologic clearance** of HPV-16/18 by intra-anal tissue swab testing
- Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in the size of peri-anal lesion(s), if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36
- Determine the humoral and cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline

3.4 ASSOCIATED SECONDARY ENDPOINT(S)

- Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC)
- **All** AEs including Serious Adverse Events (SAES), unanticipated (serious) adverse device effect (UADE), and other unexpected AEs for the duration of the study (through the Week 88 visit)
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (e.g. biopsies or excisional treatment) at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal and/or peri-anal tissue by type specific HPV testing at the Week 36 visit
- Proportion of subjects with **no evidence** of HPV-16/18 from intra-anal swab by specific HPV testing at the Weeks 36, 64, and 88 visits
- Proportion of subjects with **no evidence** of anal or anal/peri-anal LSIL or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, and PAIN3) on histology (i.e. biopsies or excisional treatment) at the Week 36
- Proportion of subjects with **no progression** of anal or anal/peri-anal HSIL to carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at the Week 36 visit
- Percent **reduction** in the number of intra-anal and/or peri-anal lesion(s) and the size of peri-anal lesion(s) if present, as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline..
- Levels of serum anti-HPV-16 and anti-HPV-18 antibody (Ab) concentrations at baseline and the Weeks 15, 36, 64, 88 visits
- Interferon- γ ELISpot response magnitudes at baseline, and the Weeks 15, 36, 64, and 88 visits
- Flow Cytometry response magnitudes at baseline and Week 15 visits

3.5 EXPLORATORY OBJECTIVE(S)

- Describe the **efficacy** of more than 3 doses of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16/18
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of more than 3 doses of VGX-3100, as measured by **virologic clearance** of HPV-16/18
- Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples
- Describe the **clearance** of HPV-16/18 infection from non-anal anatomic locations
- Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression
- Describe PRO for subjects treated with VGX-3100

3.6 ASSOCIATED EXPLORATORY ENDPOINT(S)

- Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64 for subjects who receive 4 doses of VGX-3100
- Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue for subjects who receive 4 doses of VGX-3100
- Assessment of proinflammatory and immunosuppressive elements in tissue, where feasible.
- Proportion of subjects who have **cleared** HPV-16/18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36 visit)
- HRA, cytology, and HPV test results and miRNA profile (baseline and at Weeks 15, 28, and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at the Week 36 visit
- Patient reported outcome endpoints will be obtained prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4th dose.

3.7 EFFICACY ASSESSMENT

Screening biopsies will be collected from all intra-anal and/or peri-anal lesions of adequate size (≥ 4mm). Visible lesions observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal and/or peri-anal tissue obtained from biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Tissue will be analyzed for evidence of histopathologic regression. Clearance of HPV-16/18 will be determined using the by type specific HPV polymerase chain reaction (PCR) test on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0 (prior to dosing) and Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects)

and OP rinse samples (all subjects) will be obtained at Day 0 (prior to dosing), and at Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C, Figure 2), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of the standard of care. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only. All tissue samples obtained from biopsies or removed per standard of care will be sent to the PAC for review.

3.8 SAFETY ASSESSMENT

Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the PDC.
2) All AEs including SAEs, UADEs, and for the duration of the study.

All subjects will be followed for 88 weeks.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. The following stopping rules will be applied:

- If at any time during the study one-third (1/3) or more of the subjects experience an Adverse Event of Special Interest (AESI), further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AEs) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 AEs, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, PI for the trial, IRB (if applicable) and the DSMB.
- The Sponsor or Designee will notify all Investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

3.9 IMMUNOGENICITY ASSESSMENT

Humoral and cell mediated immune responses in response to VGX-3100 treatment may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

4.0 TRIAL POPULATION

4.1 INCLUSION CRITERIA

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2[a] within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16/18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue (blocks only) provided to the Study PAC for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    i. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    i. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with follicle-stimulating hormone (FSH) level >40mIU/mL;
    ii. Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    iii. Subject agreement to avoid pregnancy one month after last dose of IP (Week 12 or Week 40);
    iv. Women of Childbearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of IP (Week 12 or Week 40). The following are acceptable methods:
        1. 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);

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

9. Men who could father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

[a] An HIV rapid test may be used given the following conditions are met: 1. The test is an antigen/antibody immunoassay, 2. The test is only done using blood, 3. The test must be performed in the office and done by qualified study staff members

4.2 EXCLUSION CRITERIA

1. Untreated micro invasive or invasive cancer[a];
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN[b];
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN[b];
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN[b];
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN[b];
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;8.Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
8. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
9. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
10. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator[c];
11. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    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, nasal, topical, 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 Tumor Necrosis Factor (TNF)-α inhibitors (e.g. infliximab, adalmumab or etanercept);
    e. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
12. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);

13. Receipt of any non-study related non-live vaccine within 2 weeks before or after any VGX-3100 dose;
14. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks before or after any VGX-3100 dose;
15. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treated as deemed by the Investigator;
16. 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);
17. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
18. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of a study dose;
19. History of seizures unless seizure free to 5 years with the use of one or fewer antiepileptic agents;
20. 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;
21. Resting heart rate <50 beats per minute (bpm) (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
22. Prior major surgery within 4 weeks of Day 0;
23. Participated in an interventional study with an investigational compound or device within 4 weeks of signing the ICF (participation in an observational study is permitted);
24. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrilator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
25. 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;
26. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;

b. Prisoner or subject who is compulsorily detained (involuntary incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

c. Active military service personnel;

d. Study-related staff or family members of study-related staff

[a] This criterion includes subjects who have microscopic or gross evidence of invasive cancer, or the suspicion of cancer in any histopathologic specimen by any pathologist at screening.

[b] When observation is the standard of care this will not exclude a subject from the study.

[c] If the lab is redrawn and the result from the redrawn sample no longer meets this exclusion criteria, then the subject is not excluded on the basis of this criterion

4.3 DISCONTINUATION/WITHDRAWAL OF TRIAL SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION FROM THE STUDY

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from further treatment with VGX-3100. Subjects will not receive further doses of VGX-3100 followed by EP but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests a Grade 3 toxicity attributable to VGX-3100/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM STUDY

Subjects who become ineligible to continue on the study based on no longer meeting the inclusion criteria should be discontinued from study treatment and managed per routine standard of care but should continue on the study without further biopsy.

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 anal or anal/peri-anal HSIL, and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls to the subject should be made and if that fails, then a certified letter is sent to the subject's last known mailing address) so that they can be considered withdrawn from the study for disposition purposes. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will the subject be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

If a subject elects to discontinue treatment/EP they should be encouraged to stay in the study and complete all follow-up visits and procedures and have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events (Table 3). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 88). A subject will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs and/or SAES present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 – Safety Parameters.

4.3.4 REASONS FOR DISCONTINUATION/WITHDRAWAL

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

- 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 AEs regardless of relation to study drug.
- Death of a subject, (including manner of death if known)
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the eCRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a maternal obstetrical or medical need to withdraw subject. Investigator must consult the Medical Monitor before withdrawing a subject from participation in the study.
- Protocol Deviation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g. treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including 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 who receive study treatment and discontinue prior to Week 36, primary endpoint procedures, then supplementation of study subjects will be considered.

5.0 TRIAL TREATMENT

5.1 INVESTIGATIONAL BIOLOGIC PRODUCT

The IP to be used in this trial is described in Table 4. The IP will be presented in a clear glass cartridge and injected intramuscularly.

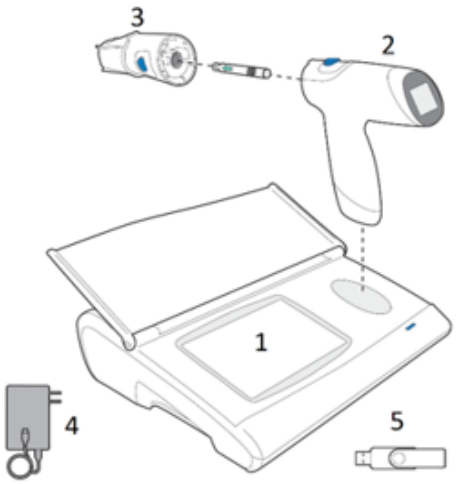
Table 4: Investigational Biologic Product

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

5.2 CELLECTRA™ 5PSP DEVICE DESCRIPTION:

VGX-3100 will be delivered using the CELLECTRA™5PSP device. The device consists of five (5) main components (see Figure 3).

Figure 3: CELLECTRA™ 5PSP Base Station with Handset



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

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

3) CELLECTRA™ 5PSP Sterile Single Use Array which consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

4) USB International Power Supply

5) Flash Drive

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset.

Handset

The handset facilitates delivery of the needles for injection and electroporation into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit and is compliant to International Ethics Committee (IEC) 62133 and UL 2054. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire.

Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 IM injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array (indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The 5PSP Array features no software.

The base station and handset with the 5PSP Array are illustrated in Figure 3.

5.3 TREATMENT REGIMEN

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-203 study will receive the same three 6 mg doses of VGX-3100 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 at Week 12. A fourth dose may be administered at Week 40.

The first study treatment will be given as soon as possible following confirmation of anal or anal/peri-anal 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.

5.4 PACKAGING AND HANDLING

Each cartridge will be labeled with a single-panel label and then individually packaged within a pouch that will contain an additional, single-panel label with tear-off. The VGX-3100 label will include, at minimum, the following information in Table 5.

Table 5: Example of Packaging and Label Information

Cartridges (primary container)	**Pouches** (secondary packaging)
LABEL VGX-3100 Insert cap end Sponsor name IM administration Investigational Use Only	**LABEL BODY** Study ID VGX-3100 Single-use cartridge containing 1 mL IM administration via CELLECTRA™ 5PSP Store at 2-8°C, expiration date Caution Statement Sponsor name and address
	LABEL TEAR OFF Study ID VGX-3100 Patient ID: _____ Date: (DD-MMM-YYYY): _____ Must be used by (time): _____

See Figure 4 below for example of CELLECTRA™ 5PSP device component labels.

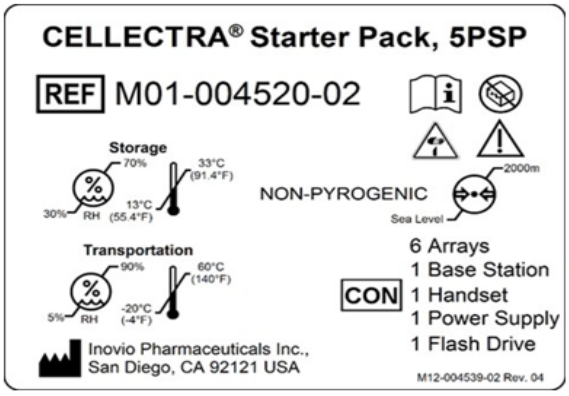
Figure 4: Examples of Device Labels (Base, Handset, Array, Outer Box)

Base Station Label

Handset Label

5PSP Array Label

Outer Box Packaging Label



5.5 HANDLING AND STORAGE OF IP AND DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual. The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and relative humidity ranges of 30-70%. The Sponsor should be notified of any deviations from this recommended storage condition. For the specific temperature guidelines for storing, please refer to the CELLECTRA™ 5PSP User Manual.

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.

5.6 PREPARATION AND DISPENSING

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. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. The Sponsor should be notified of any deviations from

this recommended storage condition. Inovio Pharmaceuticals Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Preparation and Dispensing

It is the responsibility of the Investigator to ensure that VGX-3100 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, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration.

The pouch must not be discarded until:

1. Administration is completed and
2. All pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator. If VGX-3100 is not used within this timeframe it must be discarded after reconciliation.

5.7 USE OF CELLECTRA™5PSP DEVICE

The instructions for use of the 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. Refer to the User Manual for further instruction. 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.

5.8 DRUG AND DEVICE ACCOUNTABILITY

5.8.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of IP 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;
- Date and initials of person responsible for each IP inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable

5.8.2 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The site is responsible for maintaining the device. The device must have full traceability from receipt of the products through the subject use, and the return of the device. The site must document acknowledgement of receipt and then notify INOVIO upon receipt of the device. This includes the content shipped and condition of the items upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP Base Station & Handset serial number, 5PSP 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.

5.9 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT AND CELLECTRA™ 5PSP DEVICE

5.9.1 RETURN OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at the site per the institutions policy or returned to INOVIO or its designee, if the site cannot destroy the unused IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site. Do not attempt to remove the cartridge from the array once it has been used.

It is the Investigator's responsibility to arrange for the 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 personal or designated Study Monitor.

If IP is returned to INOVIO, 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. The return of unused IP(s) should be arranged with the responsible INOVIO personnel and/or Clinical Monitor.

5.9.2 RETURN OF CELLECTRA™ 5PSP DEVICE

Upon completion or termination of the study, all investigational devices and unused components (Base, Station and Handset,) must be returned to INOVIO. Please contact an Inovio representative for specific instructions on the return of the device and components. Any unused or expired 5PSP Arrays should be destroyed on site per the site’s institutional policy. If a site’s policy does not allow for the destruction of the Arrays on site, please contact an Inovio representative for further instruction.

All device components returned to INOVIO 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.

If any component is to be 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, 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.

6.0 TRIAL 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 3).

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

Protocol waivers or exemptions will not be granted. 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 3) are essential and required for study conduct. Subject eligibility should be reconfirmed at every study visit.

6.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial subjects, explain the trial, and provide them with an ICF that describes the Screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial 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 trial 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.

6.2 BEFORE TREATMENT PROCEDURES

Subjects who consent to participate must have paraffin-embedded tissue block(s) from a previous biopsy (ies) and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the 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), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with anal or anal/peri-anal HSIL, by a local pathologist, where the initial biopsy tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, biopsy samples should be collected from all intra-anal and/or peri-anal lesions of adequate size during Screening following the consent of the subject. The 10 week Screening window begins upon collection of the biopsy sample(s) that will be evaluated by the PAC.

At Screening, subjects must have a diagnosis of histologic anal or anal/peri-anal HSIL confirmed by the PAC and intra-anal and/or peri-anal specimen test positive for HPV-

16/18 by PCR to be eligible for participation in the study (provided the subject also meets other eligibility criteria). Subjects whose intra-anal and/or peri-anal specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16/18.

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

6.2.1 SCREENING EVALUATIONS

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the HIV test which must be performed within 30 days prior to Day 0 and the safety laboratory collections/assessments and ECG, which must be performed within 45 days prior to Day 0. All Screening assessment values must be reviewed ***prior*** to study treatment. Some of these evaluations/actions will be performed again later in the trial (see later text and the Schedule of Events Table 3 for more detail).

- Signed ICF
- Medical history/demographics, including history of prior anal or anal/peri-anal HSIL
- Socio-Behavioral Assessment; including smoking history, exposure to second-hand smoke, alcohol intake history, recreational drug use and contraceptive use
- Prior concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Complete Physical Examination
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate), height, weight and body mass index (BMI) measurements
- 12-lead ECG (within 45 days prior to Day 0)
- Baseline laboratory evaluations (including complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine (Cr), glucose, alanine aminotransferase [ALT], and creatine phosphokinase [CPK]) (to be performed within 45 days prior to Day 0)
- Urine pregnancy test
- Serology (HIV Ab) within 30 days prior to Day 0
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- Digital Anal Rectal Examination (DARE)
- Lesion photography (intra-anal and/or peri-anal)
- High Resolution Anoscopy (HRA) with Biopsy (tissue must be reviewed by the PAC).

- If a historical biopsy is used with a corresponding HRA evaluation, then the HRA does not need to be repeated for Screening to determine eligibility as long as it is within the allowable window of 10 weeks.

- Whole blood (at least 68 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile must be collected **before** dosing on Day 0
  - It is acceptable to collect the blood as follows:
    - Screening: obtain 34 ml of whole blood and 4 ml of serum
    - Day 0: obtain 34 ml of whole blood and 4 ml of serum **prior** to dosing

6.3 DURING TREATMENT PROCEDURES BY VISIT

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

6.3.1 DAY 0

The following study evaluations will be performed at Day 0 (unless noted) *prior* to the first study treatment:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile (if whole blood and serum were not collected at Screening, then 68 ml of whole blood and 8 ml of serum should be drawn at this time point **prior** to dosing)
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcome (SF-36v2™ and EQ-5D-5L) (may be performed at Day -1 or on Day 0, again provided it is done **prior** to the first study treatment)
- Study treatment administration

The following evaluations will be performed on Day 0 after study treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment

- Distribute Participant Diary Card (PDC)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during the phone call:

- Review Day 0 of 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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.3 WEEK 4 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant mediation review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Collect and review PDC for dose 1
- Study treatment administration

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

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

Patient reported outcomes (SF-36v2™ and EQ-5D-5L) ****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during the phone call:

- Review of PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.5 WEEK 12 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect and review PDC for dose 2
- Study treatment administration

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

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

****Please remember to download EP data from the CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

6.3.6 WEEK 15 (± 1 WEEK)

The following study evaluations will be performed at Week 15:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA
    - 51 ml of whole blood and 4 ml serum should be drawn at this time point
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab

- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.7 WEEK 28 (± 1 WEEK)

The following study evaluations will be performed at Week 28:

- Reconfirm subject eligibility
- Concomitant medical review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)

6.3.8 WEEK 36 (± 1 WEEK)

The following study evaluations will be performed at Week 36:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swabs

- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.9 WEEK 40 (± 1 WEEK)

The following study evaluations will be performed at Week 40:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Study treatment administration
- Based on biopsy results collected at Week 36 and Investigator judgment, a 4th dose may be given at this visit

****Please remember to download EP data from CELLECTRA™ 5PSP device within 24-48 hours of study treatment.****

The following study evaluations will be performed at the Week 40 post treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Patient reported outcomes:- the two "global" questions and SF-36v2™ and EQ-5D-5L

6.3.10 8-14 DAYS POST DOSE 4 PHONE CALL (FOR SUBJECTS WHO RECEIVED A 4TH DOSE)

The following information will be evaluated during the phone call:

- Review PDC for dose 4 (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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.11 WEEK 64 (± 2 WEEKS)

The following study evaluations will be performed at Week 64:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment (only for subjects who received a 4th dose at Week 40)
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.12 WEEK 88 (± 2 WEEKS)

The following study evaluations will be performed at Week 88:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Full Physical assessment
- Urine pregnancy test
- Vital signs
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE

- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.4 TRIAL PROCEDURES

6.5 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all trial-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., ANUS01001). 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.

6.6 DEMOGRAPHICS

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

- Age
- Gender
- Race/ethnicity
- Dominant hand/arm

6.7 SAFETY EVALUATIONS

6.7.1 PHYSICAL EXAM

A full Physical exam (PE) will be conducted during Screening and study discharge (Week 88). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems, and a DARE. All assessments not completed should be marked as not done.

A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

6.7.2 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 prior to measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.7.3 HEIGHT AND WEIGHT

Weight and height will be collected at all dosing visits in order to calculate the BMI.

6.7.4 MEDICAL HISTORY

Medical history, including history of prior anal or anal/peri-anal dysplasia and gynecologic history will be obtained at Screening. For females, previous history of treatment for VIN, CIN and/or VAIN will be collected. All relevant past and present conditions, as well as prior surgical procedures at least 6 months prior to enrollment will be recorded for the main body systems.

6.7.5 SOCIO-BEHAVIORAL ASSESSMENTS

Socio-Behavioral Assessment, including self-reporting of the following: smoking history, history of exposure to second-hand smoke, alcohol intake history, recreational drug use history, history of contraceptive use and type of contraceptive if known, reproductive history, sexual preference and sexual practices history, and pregnancy history will be obtained at Screening.

At Weeks 36, 64 (only for subjects who receive a 4th dose), and 88, a socio-behavioral assessment will be performed to document any changes from Screening and/or other time periods.

6.7.6 LABORATORY EVALUATIONS

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

Complete Blood Count:

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

Serum Chemistry:

- Glucose
- Blood urea nitrogen
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase

6.7.7 PREGNANCY TESTING

For women of reproductive potential, a negative spot urine pregnancy test is required at Screening, and prior to each study treatment, HRA, DARE and surgical excision or biopsy.

6.7.8 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.

6.7.9 PARTICIPANT DIARY CARD (PDC)

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 11:59pm)
- 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 days post dose phone calls and at the next in-person visits.

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 criteria for a Grade 1 or higher AEs should be documented as an AE 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.

6.8 INJECTION AND ELECTROPORATION (EP)

Subjects will receive at least three doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by IM injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 5PSP. A fourth dose is optional for those assessed to be partial responders at the Week 36 efficacy assessment. Study treatment plus EP must not be given within 2 cm of a tattoo, keloid or hypertrophic scar, or if there is implanted metal within the same limb. EP may not be performed in the same arm adjacent to an implantable medical device (e.g., cardiac pacemaker, defibrillator or retained leads following device removal). The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, and at Week 40 (for Subgroup C, Figure 2 only). Please refer to the Investigator's Brochure for further information.

6.9 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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, and Weeks 4 and/or Week 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.

6.10 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 into the study as listed in the Schedule of Events (Table 3).

6.11 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

The injection site will be assessed by study personnel prior to and between 30-45 minutes after each study treatment. Subjects will be advised to record local and systemic AEs for 7 days after each study treatment on a PDC which will be reviewed with study personnel 8 – 14 days after doses 1 and 2, Week 15, and 8-14 days after dose 4 (if applicable).

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any AEs, 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 AEs will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's Case Report Form (CRF).

6.12 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 6.

Table 6: 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 "Food and Drug Administration (FDA) Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" *In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

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

6.13 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, PRO instruments will be administered. The following PRO questionnaires will be used:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [25]. SF-36v2™ will be administered at the following time points:
  - Day 0 (*before* the first study treatment)
  - 8-14 days post dose 1
  - Week 4 (post dose 2)
  - 8-14 days post dose 2
  - Weeks 12 (post dose 3), 15, 36, 40
  - 8-14 days post dose 4* (only for those who received a 4th dose)
  - Weeks 64, 88
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [26, 27] and will be administered as described below:
  - Day 0 (*before* the first study treatment)

- 8-14 days post dose 1
- Week 4 (post dose 2)
- 8-14 days post dose 2
- Weeks 12 (post dose 3), 15, 36, 40
- 8-14 days post dose 4* (only for those who received a 4th dose)
- Weeks 64, 88

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

- **Additional Global PRO Questions-** regarding quality of life after surgery or biopsy. These two questions will be administered at Week 40 only.

6.14 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (Screening and Day 0 prior to dosing) and at Weeks 15, 36, 64 and 88. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding enzyme-linked immunosorbent assay (ELISA) may be performed to measure the anti–HPV-16/18 Ab response induced by VGX-3100.

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

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 and Weeks 15 and 36. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

6.15 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then the relevant paraffin blocks may be collected for the assessment of proinflammatory and immunosuppressive elements. . Assessment of markers may include, but are not limited to, CD8+ and FoxP3+ infiltrating cells as well as Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.16 ANAL AND/OR PERI-ANAL HPV TESTING

All intra-anal and/or peri-anal lesions of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL sites(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Intra-anal and/or peri-anal swabs will undergo HPV testing using a PCR based assay, SPF10.

The subject will be requested to abstain from sexual activity and refrain from the use of douching to eliminate potential interference with the results of HPV testing.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 in ThinPrep™ collection media. The HPV Cobas test will be performed on the ThinPrep™ specimens at Screening, and Weeks 36 and 64 when applicable. Anal cytology will be performed on intra-anal samples. At each of these visits, a recent history will be collected via self-report.

6.17 HPV TESTING FROM OTHER ANATOMICAL SITE (NON-ANAL)

Vaginal, cervical (female subjects), penile (male subjects), and OP rinse samples (all subjects) will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess virologic clearance at non-anal sites using a PCR based HPV assay. All samples will be read in a central laboratory.

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

6.18 ANAL PHOTOGRAPHS AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of anal or anal/peri-anal HSIL confirmed by the PAC at Screening. Subjects will undergo HRA at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 to identify all intra-anal lesion(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Investigators should follow Table 1: Minimally Required Procedure at each Biopsy Visit for the Weeks 36 and 64 biopsies.

Photography of all qualifying intra-anal and/or peri-anal lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

If the intra-anal and/or peri-anal tissue sample(s) result suggests progression to cancer, the Investigator may schedule an ad hoc visit to perform HRA and possible biopsy if clinically indicated.

6.19 UNSCHEDULED BIOPSIES

Unscheduled biopsies may be performed on new lesions or suspected progression of original lesions per the Investigator's medical judgment during the study. 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. All biopsy samples/excised tissue (including standard of care) will be sent to the central pathology lab for review by the PAC.

6.20 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 eCRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to the 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 eCRFs. 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 eCRF.

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, nasal, topical, 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.

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.

6.21 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, including illicit drugs, taken to the Investigator and/or other study personnel. To remain in the study, illicit drugs should not be taken.

Subjects should refrain from becoming pregnant until one month following the last dose of IP (Week 12 or Week 40) by using appropriate contraceptive measures (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

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

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

As a requirement for inclusion in the HPV-203 study, Investigators will only be chosen if they are experienced in the management of anal cancer, and are experienced in performing HRA.

HPV-203 Investigators are instructed to perform additional, ad hoc HRA exams and biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analyses. These additional measures should minimize the risk of progression of anal or anal/peri-anal HSIL and the risk of harboring an undiagnosed occult early invasive anal or anal/peri-anal cancer. The frequency of close monitoring by experienced Investigators should minimize the risk of cancer progression during the study and the additional measures are beyond what is expected in standard of care.

7.2 ADVERSE EVENTS (AEs)

An 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 AEs 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 eCRF, including the event's seriousness, severity, action taken, and relationship to IP. Adverse Events should be followed until resolution or stable and the outcome will be documented on the appropriate eCRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

Adverse Events 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 increased 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 demise, still birth, congenital anomaly of fetus/newborn);
- AEs that occur from the study Screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE;
- Conditions that lead to a medical or surgical procedure.

Adverse Events do not include the following:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE;
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the Screening visit that do not worsen;

- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions);
- Overdose without clinical sequelae;
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history eCRF;
- Uncomplicated pregnancy;
- An induced elective abortion to terminate a pregnancy without medical reason.

7.3 SERIOUS ADVERSE EVENTS

A SAE is any AE that meets one of the following conditions:

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

Classification of Serious Adverse Events:

- Death is an outcome of an AE, and not an SAE in and of itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.15.

7.4 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose; for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the AEs. An AE 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 ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of serious expected AEs, 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

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 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 eCRF at the maximum severity reported.

The Investigator will grade laboratory AEs and clinical AEs or SAEs with respect to the following levels of severity as per CTCAE v 4.03 for applicable patient populations:

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

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

7.7 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable causal relationship to the administration to either or both IP and/or the CELLECTRA™ 5PSP device. The Investigator will assess causal relationship of the AE separately to each of the investigational drugs and also the investigational device. The reasonable causal relationship means that there are facts (evidence) or arguments to suggest a causal relationship. An AE may also be assessed as not related to either or both IP and/or investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs 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 AE 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 VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation or deemed clinically significant by the Investigator must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, and 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 Sections 7.2 and 7.3. 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 is assessed as detailed in Section 7.6.

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT).

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines not only the severity of the event but also whether the abnormality in question is "clinically significant (CS)" or "NCS." CTCAE v. 4.03 grading criteria can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.9 POST-TRIAL 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 probably or possibly related to the study treatment, he/she should promptly document and report the event to the Sponsor.

7.10 PROCEDURES FOR DOCUMENTING PREGNANCY DURING THE TRIAL

Should a subject become pregnant after enrolling in the study, she will not be given any further treatments with the IP. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax or email, as described in Section 7.15. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further 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 Sponsor.

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.11 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 88.

The sources of AEs cover:

1. The subject's response to questions about his/her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate eCRF.

Any SAE occurring during the course of the study must be reported to the Sponsor within 24 hours of awareness.

7.12 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 AEs classified by system organ class (SOC), preferred term, severity, and relationship to study treatment;
- Changes in safety laboratory parameters (e.g., hematology and serum chemistry);
- 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.

7.12.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

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

As per the Toxicity Grade for Healthy Adults, the most severe grade for that particular event is to be documented in the eCRFs.

Sites will inform the Sponsor via method described in Section 7.15 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.13 ADVERSE EVENT REPORTING

To assure the safety of the participants, information about all AEs (see Section 7.2), whether volunteered by the subject, discovered by the 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.

7.14 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited AEs will be collected throughout the study and recorded in the Electronic Data Capture (EDC) system. The Study Report will analyze and summarize all AEs throughout the study. Emphasis will be placed on the following:

1. Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately

2. Unsolicited AEs will be collected and summarized for the entire study period

7.15 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS AND AESIS

The reporting period for SAEs (without regard to causality or relationship) and AESIs is comprised of the period following the signing of the ICF through Week 88. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator will complete the SAE/AESI Report form and report the event to the Sponsor within 24 hours of becoming aware of the event. The Investigator may also directly report this event to the IRB/EC according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.5 (UADE) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant 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.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the Investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the Investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION

MEDICAL MONITOR: [redacted], M.D., Ph. D.
EMAIL: [redacted]

SAE REPORTING INFORMATION

EMAIL: safety.inovio@apcerls.com
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is an attachment to an e-mail message, to the email address as indicated above. Any SAE supporting documents provided by facsimile (Fax) are to include a coversheet that identifies the reporter name and contact information of the study site.

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.

In addition to providing the SAE report to the Sponsor or designee within 24 hours of becoming aware of the event, the AE that is serious must be recorded in the AEs eCRF. The entry into the eCRF is required to be done as soon as possible.

The Investigator will supply the Sponsor and the IRB/EC with more information as it becomes available and any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

When recording the SAE form, correct medical terminology/concepts are to be used and the use of abbreviations and colloquialisms are to be avoided.

Serious Adverse Events 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.

In the event of a pregnancy, the Investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

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 experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.4 and 7.16).

7.17 REPORTING OF CELLECTRA™5PSP DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported within 24 hours of becoming aware of the event per Sections 7.2 and 7.3.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during

the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form provided must be completed and emailed to the Sponsor at clinicalcomplaint@inovio.com.

Additional instructions on complaint reporting to be provided separately.

7.18 TRIAL DISCONTINUATION

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

Should the trial be terminated and/or the site closed for any reason, all investigational drugs & devices must be returned to INOVIO or its representative. The PI should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 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 or its representative.

This is a single-arm, multi-center, open-label clinical trial of VGX-3100 in subjects with a diagnosis of AIN2, AIN3, PAIN2, or PAIN3 associated with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of AIN/PAIN HSIL and viral clearance of HPV-16/18 based on tissue collected at Week 36. The primary hypothesis is that the treatment will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16/18 infection, complete regression, non-progression, and anatomic extent. Other secondary analyses concern safety and humoral and cellular immunological measures. Exploratory efficacy analyses concern extended dosing with respect to regression, clearance, clearance among non-anal anatomic locations, and association of miRNA profile, anoscopy, cytology, and virology with efficacy. Other exploratory analyses pertain to tissue immunological measures and PRO.

8.3 STATISTICAL HYPOTHESES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations are:

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: p≤ 0.15 vs. H1: p > 0.15.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.05 and the corresponding lower bound of the one-sided 95% CI exceeds 0.15.

For the analysis, the efficacy time frame is defined by any time starting from 14 days prior to the -specified visit week.

8.5.2 SECONDARY ANALYSES

The secondary efficacy binary 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.

The anatomic extent endpoint will be analyzed by calculating the mean percent change in surface area and the mean percent change in number of lesions and associated 95% t-distribution based confidence intervals.

Post-baseline ELISA titers will be summarized with geometric mean and associated 95% CIs. Post-baseline increases in ELISPOT and Flow responses will be summarized with tobit-based means and 95% CIs. Valid samples for statistical analysis purposes will be those collected within 14 days of the specified visits. Baseline is defined as the last measurement prior to the first treatment administration.

8.5.3 SAFETY ANALYSES

All AEs will be summarized among the safety population by frequency. These frequencies will be presented overall and separately by dose, and will depict overall, by SOC 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 AE data will be based on events occurring within 28 days following any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days following any dose and regardless of when they occurred.

8.5.4 DISPOSITION

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

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables for the mITT population.

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

Prior medications are those that were used and stopped 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. Data for all prior medications will be summarized with percentages for the mITT population.

8.5.6 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 will not be adjusted for possible early stopping due to futility.

8.5.7 MULTIPLICITY

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

8.5.8 MISSING VALUES

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.

No other missing data will be imputed or replaced.

8.5.9 EXPLORATORY ANALYSES

The exploratory efficacy binary 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.

Other analyses will examine the relationship between the primary efficacy endpoint and a) miRNA results, b) HRA results, c) cytology results, and d) HPV results. Relationships will be examined with contingency tables and/or logistic regression models which model the primary endpoint versus these results as regressor variables.

The change in tissue immune response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.6 SAMPLE SIZE/POWER

A sample of 24 subjects provides ~80% power to declare superiority over historical control, assuming the true proportion of subjects who achieve the primary endpoint is 40% for the treatment arm versus 15% for the historical control, and that 90% are evaluable at Week 36 from 1st dose.

8.7 RANDOMIZATION AND BLINDING

This is an open-label trial, and therefore, site personnel, individual subjects and INOVIO or its representative trial personnel will be aware of the treatment allocations for this trial. Randomization does not apply.

9.0 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical trial 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

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., ICF, 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:

- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.

- Maintain a file of trial-related information (refer to trial files) that include all correspondence with the IRB/EC.
- Notify the IRB/EC when the trial is completed (i.e. after the last visit of the final trial subject).
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.

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 OFFICE OF BIOTECHNOLOGY ACTIVITIES

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 [NIH] Office of Biotechnology Activities [OBA]) governing research that involves recombinant or synthetic nucleic acid.

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 trial, 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 (Section 6.1).

9.5.2 COMPLIANCE WITH IRB/EC REQUIREMENTS

This trial 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 trial 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.

9.5.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURE REGULATIONS (21CRF PART 11)

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

9.5.5 COMPLIANCE WITH PROTOCOL

Subjects will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviation (PD),

should a deviation be discovered, Sponsor must be informed immediately. Any PD 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 prior review and documented approval/favorable opinion from the Sponsor and IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects. While every effort should be made to avoid PD, should a deviation be discovered, Sponsor must be informed immediately. Any PD impacting Subject safety must be reported to the Medical Monitor immediately.

10.0 DATA COLLECTION, MONITORING, AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial 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 trial Sponsor, the governing health authorities or the FDA, if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

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

Information about trial subjects will be kept confidential and managed in accordance with the requirements of the HIPAA of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

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

11.0 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 trial.

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.

Case Report Form will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified with an SID.

It is the Investigator's responsibility to retain trial essential documents for at least two (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 two (2) years have elapsed since the formal discontinuation of clinical development of the IP. 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.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY AND QUALITY MONITORING

An independent 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 there appears to be a regression with VGX-3100.However, no formal interim analysis will be performed.

12.2 PATHOLOGY ADJUDICATION COMMITTEE

All anal biopsies will be read by a central expert PAC to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion. The logistics and details of the PAC are detailed in the PAC Charter.

12.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:
    - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
    - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.
    - Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Assure that the trial facilities continue to be acceptable.
    - Compare the trial eCRFs 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.

13.0 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 at least 60 days prior to submission for publication. The Sponsor will have 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) will 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 US Patent and Trademark Office and/or foreign patent office(s).

14.0 LIST OF ABBREVIATIONS

Ab	Antibody
ADR	Adverse Drug Reaction
AEs	Adverse events
AESI	Adverse Event of Special Interest
AIN	Anal Intraepithelial Neoplasia
AIS	Adenocarcinoma-in-situ
ALT	Alanine Aminotransferase
BMI	Body Mass Index
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIN	Cervical Intraepithelial Neoplasia
CIN1	Grade 1 Cervical Intraepithelial Neoplasia
CIOMS-I	Council for International Organizations of Medical Sciences
Cr	Creatinine
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CPK	Creatine Phosphokinase
DARE	Digital Anal Rectal Examination
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
ELIspot	Enzyme-linked Immunospot Assay
EP	Electroporation with CELLECTRA™5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ER	Emergency Room
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
gbm	gay and bisexual men
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HRA	High-resolution Anoscopy
HR-HPV	High-risk HPV Type
HSIL	High Grade Squamous Intraepithelial Lesion
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug
INOVIO	Inovio Pharmaceuticals, Inc.

IP	Investigational Product
IRB	Institutional Review Board
IRB/IEC	Institutional Review Board or Independent Ethics Committee
ISO	International Organization for Standardization
LAST	Lower Anogenital Squamous Terminology
LSIL	Low Grade Squamous Intraepithelial Lesion
miRNA	MicroRNA
mITT	Modified Intent to Treat
MSM	men who have sex with men
NCS	Not Clinically Significant
OBA	Office of Biotechnology Activities
OP	Ororpharyngeal
PAIN	Peri-anal Intraepithelial Neoplasia
PAM	Protocol Administrative Memo or Letter
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIN	Penile Intraepithelial Neoplasia
PP	Per Protocol
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PE	Physical Exam
PRO	Patient-reported Outcome
SAEs	Serious Adverse Events
SF-36v2™	36-Item Short Form Health Survey
SID	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPANC	Study of the Prevention of Anal Cancer
SSC	Saline Sodium Citrate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumor Necrosis Factor
UADE	Unanticipated (Serious) Adverse Device Effect
US	United States
VAIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
WFI	Water for Injection
WOCBP	Women of Childbearing Potential

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16.0 APPENDICES

HPV-203

A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal, High grade squamous intraepithelial lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 13683

Protocol Version: 3.0
Protocol Version Date: 22January2020

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 2.0 dated 14 May 2019 to Version 3.0 dated 22January2020. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Effective 17July2019, the medical Monitor for HPV-203 is Dr. [redacted]. This has been previously addressed in PAM #6 (18July2019) and is now incorporated into this amendment. Dr. [redacted] contact information is as follows:
   [redacted], M.D., Ph.D.
   Email: [redacted]

2. Clarifying language regarding the download of EP data from the CELLECTRA™ 5PSP Device has been added. The language in Protocol Version 2.0 instructs sites to download EP data from the CELLECTRA™ 5PSP device within 24 to 48 hours of study treatment. This timeframe is no longer required and therefore, the new language for Protocol Version 3.0 is as follows: Following each treatment with VGX-3100, data should be downloaded from the EP device, and the data file that is created should be sent to Inovio Pharmaceuticals Inc. or designee. Instructions on how to download the data and contact information will be provided in the User Manual and during training. This has been clarified in PAM #6 (18July2019) and is now incorporated into this amendment.

3. Section 3.8 of the protocol has been updated to reflect the revised stopping rules for all studies within the VGX-3100 program. This change accounts for the verification process required following the entry of an adverse event into the database.

4. Responder and non-responder definitions for the secondary and exploratory endpoints have been provided in the Clinical Protocol Synopsis.

5. The Primary Endpoint has been updated to remove “qualifying lesions.” As a result, Footnote 8 has been revised to define intra-anal and/or peri-anal lesion tissue for Primary Endpoint and states: An intra-anal and/or peri-anal lesion evaluated by the Pathology Adjudication Committee (PAC). Please refer to revision #16 which states that the primary endpoint will be analyzed based a) all lesions and b) on qualifying lesions and new lesions.

6. The definition for qualifying lesions has been moved from Footnote 8 to Footnote 12 and states: An intra-anal and/or peri-anal lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed anal or anal/peri-anal HSIL evaluated by the Pathology Adjudication Committee (PAC).

7. Secondary objective #9 has been added to evaluate the efficacy of three doses of VGX-3100 with respect to histopathologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18, as HPV-16/18 associated HSIL is considered a significantly higher risk for anal cancer.

8. The associated secondary endpoints 8a and 8b from Protocol Version 2.0 of the have been moved and are now associated exploratory endpoints 9a and 9b in Protocol Version 3.0.

9. Associated secondary endpoint #4 has been revised to remove Week 64 and 88. Week 64 and 88 have been added to the corresponding associated exploratory endpoint #4.

10. Exploratory objective #4 has been added to describe the long term efficacy of VGX-3100, as measured by virologic clearance of HPV-16 and/or HPV-18 by intra-anal swab testing. This will correspond to secondary objective #4.

11. Exploratory objective #10 has been added to determine the long term efficacy of more than three doses of VGX-3100 with respect to the treatment of HPV-16 and/or HPV-18 to correspond with Secondary objective #9.

12. Section 5.4 has been revised to add an updated 5PSP Array Label as well an updated Outer Box Packaging Label.

13. Section 5.5 previously stated: The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and relative humidity ranges of 30-70%. The requirements have been revised removing the relative humidity range of 30-70% portion of the statement. The protocol will now state: The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and kept dry.

14. Section 6.12 Assessment of Injection Site Reactions has been updated to clarify the timeframe around daily activity for grading injection site reactions in **Table 11**. The Sponsor defines timeframe for 'daily activity' is an impact lasting 24 hours or more.

15. The following changes have been made to the Schedule of Events (**Table 8**):

    - Blood Immunologic testing will no longer take place at Week 64 given that the Week 88 immunologic testing is considered sufficient. Blood immunologic testing at Week 64 as has been removed.
    - A footnote has been added with the following language to ensure that virology and pathology are obtained on all visible lesions at Week 64: In additional to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC.

16. Language has been added to Section 8.5.1 (Primary Analysis) to indicate that the primary endpoint will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions.

17. Language has been added to Section 8.5.2 (Secondary Analyses) to indicate that all of the efficacy binary endpoints will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions. This section has also been updated to remove language relating to post-baseline ELISA titers and post-baseline increases in ELISPOT as this has been moved to Section 8.5.9 (Exploratory Analyses).

18. Language has been added to Section 8.5.9 (Exploratory Analyses) to indicate that all of the efficacy binary endpoints will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions. Language has also been added to

indicate that binary endpoints of Week 64 and Week 88 will be analyzed in two ways: a) overall and b) according to three or four doses received. This section has also been updated to move from Secondary Analysis: post-baseline ELISA titers will be summarized with geometric means and associated t-distribution based 95%CIs; post baseline increases in ELISPOT will be summarized with median and 95% CIs.

19. **Table 1** (Minimally Required Procedure at each Biopsy Visit) has been updated to indicate that new lesions or lesions that did not qualify at baseline should be biopsied at evaluation. In addition, Language has been added throughout to clarify that under Protocol Version 3.0, all visible lesions should be biopsied at the Week 64 Visit to ensure that a comprehensive assessment is done.

Medical Monitor Approval Page

Drug: VGX-3100

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

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

Approval Signature:

[redacted]

Inovio Pharmaceuticals

[redacted]

Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board/Ethics committee approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 (IRB/IEC) 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 International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

<Insert Principal Investigator Printed Name>	Date (dd/Mmm/yyyy)

Site Number: _____

Site Name: _____

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal High-Grade Squamous Intraepithelial Lesions, HSIL (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2
Protocol Number: HPV-203
Trial Phase: 2a
Estimated Number of Trial Centers and Countries/Regions: Approximately 3 study centers located in North America
Formulation: VGX-3100
Trial Design: Multi-center, single-arm, open-label phase 2 study
Criteria for Evaluation: To provide a treatment to regress anal or anal/peri-anal HSIL and clear the related HPV-16 and/or HPV-18 (HPV16/18) in individuals that are seronegative for HIV-1/2. **Research Hypothesis:** VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal HSIL[1], (AIN2[2], AIN3[3], PAIN2[4], PAIN3[5]) associated with HPV-16 and/or HPV-18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.
Dose of VGX-3100: 6 mg (1mL)
Administration: Intramuscular injection followed by EP
VGX-3100 Dosing Schedule: Day 0, Week 4 and Week 12 with one additional dose given to partial responders at Week 40
Study Duration: 88 Weeks
Primary Objective: Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18.
Primary Endpoint: Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL[6] on histology (i.e., collected via biopsy or excisional treatment)[7]and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue [8].

[1] High-grade Squamous Intraepithelial Lesion
[2] Grade 2 Anal Intraepithelial Neoplasia
[3] Grade 3 Anal Intraepithelial Neoplasia
[4] Grade 2 Peri-anal Intraepithelial Neoplasia
[5] Grade 3 Peri-anal Intraepithelial Neoplasia
[6] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.
[7] A treatment responder is defined as a subject with no histologic evidence of anal or anal/peri-anal HSIL and no evidence of HPV-16 or HPV-18 in anal lesion tissue and who did not receive any non-study treatment of curative intent of intra-anal and/or peri-anal lesions. A treatment non-responder is defined as a subject with histologic evidence of anal or anal/peri-anal HSIL, adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma or a subject with evidence of HPV-16/18 in anal lesion tissue or a subject who received non-study treatment of curative intent of intra-anal and/or peri-anal lesions.

[8] An intra-anal and/or peri-anal lesion evaluated by the Pathology Adjudication Committee (PAC).

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC). 1b. **All** adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study (through the Week 88 visit)
2. Determine the **efficacy** of three doses of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (e.g. biopsies or excisional treatment) at Week 36
3. Determine the **efficacy** of three doses of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue	3. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18[9] from intra-anal and/or peri-anal tissue by type specific HPV testing at Week 36
4. Determine the **efficacy** of three doses of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal swab testing	4. Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal swab by specific HPV testing at Week 36
5. Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue	5. Proportion of subjects with **no evidence**[10] of anal or anal/peri-anal Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, PAIN3) on histology (i.e. biopsies or excisional treatment) at Week 36
6. Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL	6. Proportion of subjects with **no progression**[11] of anal or anal/peri-anal HSIL to carcinoma from baseline to histology (i.e. biopsies or excisional treatment) at Week 36
7. Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal qualifying lesion(s), as applicable **and** the reduction in size of peri-anal lesion(s) if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36	7. Percent **reduction** in the number of qualifying[12] intra-anal and/or peri-anal lesion(s), and the reduction in size of peri-anal lesion(s) as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline[13].
8. Determine the cellular immune response following dose 3 and compared to baseline	8. Flow Cytometry response magnitude at baseline and Week 15

9. Determine the **efficacy** of three doses of VGX-3100 with respect to histopathologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18	9. Proportion of subjects with no **histologic evidence of anal or anal/peri-anal HSIL** by histology (i.e., collected via biopsy or excisional treatment) or **no evidence of HPV-16/18** at Week 36 from intra-anal and/or peri-anal lesion tissue

[9] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[10] No evidence of anal or anal/peri-anal HSIL is defined as normal tissue or anal or anal/peri-anal LSIL.
[11] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[12] An intra-anal and/or peri-anal lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed anal or anal/peri-anal HSIL evaluated by the Pathology Adjudication Committee (PAC).
[13] Baseline photographic imaging is defined as photographs obtained pre-biopsy at Screening, or post biopsy at Screening (for subjects with historical biopsy tissue).

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the long term **efficacy** of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16 and/or HPV-18	1. Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16/18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
2. Describe the long term **efficacy** of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL	2. Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64
3. Describe the long term **efficacy** of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue	3. Proportion of subjects with **no HPV-16/18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
4. Describe the long term **efficacy** of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal swab testing	4. Proportion of subjects with **no evidence of HPV-16 and/orHPV-18** from intra-anal swab by specific HPV testing at Week 64 and Week 88
5. Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples	5. Assessment of proinflammatory and immunosuppressive elements in tissue, where feasibile[14]
6. Describe the **clearance** of HPV-16 and/or HPV-18 infection from non-anal anatomic locations	6. Proportion of subjects who have **cleared** HPV-16 and/or HPV-18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36)
7. Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression	7. HRA, cytology, and HPV test results and miRNA profile (baseline and at the Weeks 15 and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at Week 36
8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100	8. Patient reported outcome (PRO) endpoints prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an

	additional PRO assessment at Week 40 if a subject receives a 4th dose
9. Determine the humoral and cellular immune response following dose 3 and additional time points compared to baseline	9a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline and Weeks 15, 36, and 88 9b. Interferon-γ ELISpot response spot forming units (SFU) at baseline and Weeks 15, 36, and 88
10. Determine the long term **efficacy** of VGX-3100 with respect to histopathologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18	10. Proportion of subjects with **no histologic evidence of anal or anal/peri-anal HSIL** on histology (i.e., collected via biopsy or excisional treatment) **or no evidence of HPV-16 and/or HPV-18** at Week 64 from intra-anal and/or peri-anal lesion

[14] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possible other relevant markers identified in the literature as sample allows.

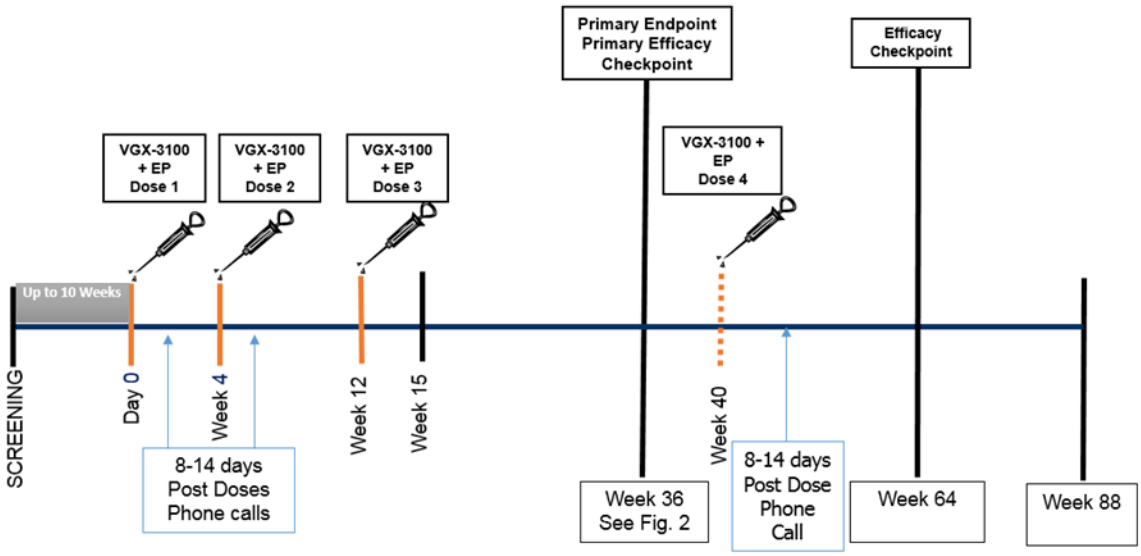
Study Design:

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or HPV-18.

Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40.

All subjects are scheduled to be followed to Week 88.

Figure 1: HPV-203 Study Visit Schedule



Biopsy(ies) will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Subjects must also have intra-anal and/or peri-anal lesion(s) tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

Visualization of the lesion and digital anal rectal examination (DARE) alone are insufficient evidence to confirm disease regression. Disease regression will be primarily based on histopathologic assessment at Week 36 and additionally assessed at Week 64. Subjects will be monitored during the course of the study by DARE and HRA. Intra-anal lesion(s) will be assessed at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 using HRA. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

The decision process following the results of the Week 36 biopsy are described below in ***Figure 2*** and are as follows: At Week 36, the subject will undergo repeat intra-anal and/or peri-anal punch biopsies of all HSIL lesions confirmed by the PAC at Screening of adequate size (≥ 4mm). (See **Table 1** Minimally Required Biopsy Procedures). If after evaluation of the biopsy tissue(s) by the PAC there is no evidence of HSIL (defined by Subgroups A or B), the subject will continue to Week 64 for HRA and undergo biopsies of the same areas (HSIL lesions) as the baseline biopsies. Any other visible lesions should also be biopsied at the Week 64 visit. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only.

Figure 2: Decision process at Week 40

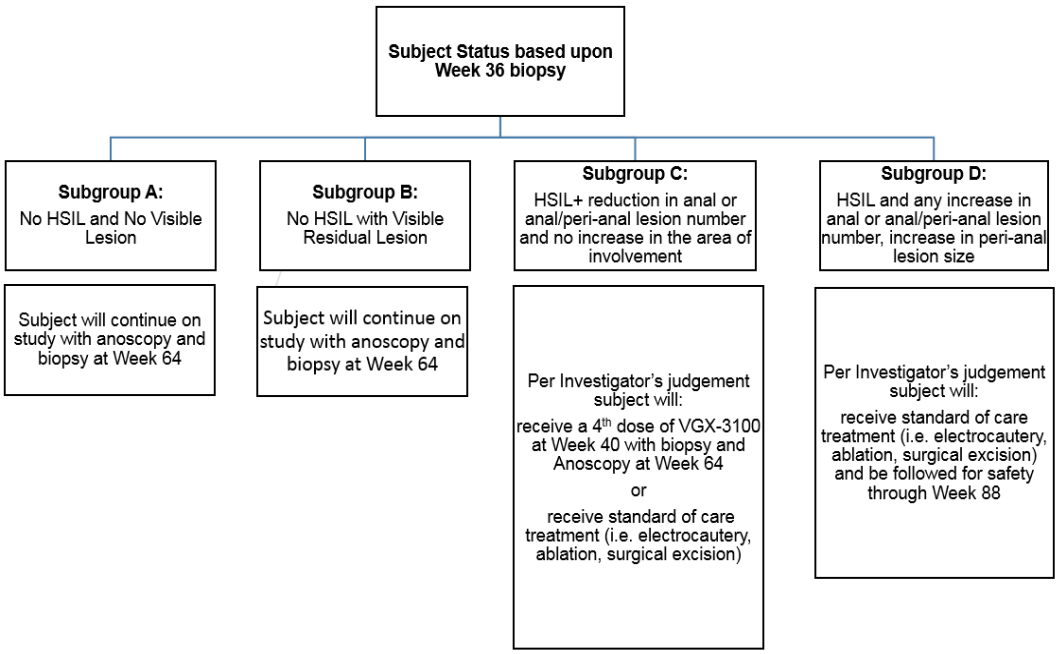


Table 1: Minimally Required Procedure at each Biopsy Visit

Pre-biopsy High Resolution Anoscopy Finding	Minimally required procedure
No lesion	Punch biopsy and photography; biopsy should be collected from within the approximate original boundaries of the study entry HSIL as proximal as possible to the original biopsy site which was previously determined to be HSIL by the PAC. New lesions or lesions that did not qualify at baseline should be biopsied at evaluation.
Single lesion (which was also present at baseline)	Punch biopsy and photography; biopsy should be collected within the boundaries of the original lesion and from the area most suspicious for advanced disease within the lesion by clinical exam. New lesions or lesions that did not qualify at baseline should be biopsied at evaluation.
Multiple lesions	Punch biopsies and photography; biopsy should be collected from the same lesions diagnosed as HSIL from study entry and from the area most suspicious for advanced disease within the lesion by clinical exam. New lesions or lesions that did not qualify at baseline should be biopsied at evaluation.

If HSIL is diagnosed in any Week 36 biopsy, but there is a reduction in the number of intra-anal and/or peri-anal lesion(s), reduction in peri-anal lesion(s) size or no change in peri-anal lesion(s) size from baseline (defined by Subgroup C), the Investigator has the option to administer a 4th dose of VGX-3100 at Week 40, and the subject will continue on the study to have HRA and biopsy at Week 64 of all lesions (qualifying and any other visible), i.e. the second efficacy checkpoint. Alternatively, the Investigator may instead choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of standard of care.

In the event of worsening anal or anal/peri-anal HSIL at any time during the trial (defined as any increase in lesion(s) area from baseline or worsening of anal or anal/peri-anal HSIL to cancer), the subject may receive standard of care treatment (i.e. electrocautery, ablation, surgical excision) per the Investigator's judgment but will continue on the study through Week 88 with HRA, but without further biopsy unless it is part of the standard of care.

If there is histologic progression to carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment but will continue through Week 88 with HRA, but without further biopsy unless it is part of the standard of care. The event will be reported as an SAE per Section 7.3. If wide excision is required, the sample(s) obtained will be sent to the PAC for evaluation.

Efficacy Assessment:

Screening biopsies will be collected from all intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm). Visible lesion(s) observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and/or HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal tissue, utilizing HRA with biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. In addition to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and samples to be sent to the central pathology lab for PAC review. Tissue samples will be analyzed for evidence of histopathologic regression. Clearance of HPV-16 and/or HPV-18 will be determined using the type specific HPV PCR test on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be collected at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) rinse samples will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only.

Immunogenicity Assessment: Humoral and cell mediated immune responses to VGX-3100 may be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 36, and 88. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

Virologic Assessment: Intra-anal and/or peri-anal swabs will be obtained to characterize HPV infection at Screening, Day 0, and Weeks 4, 15, 28, 36, 64 and 88. Likewise, PCR-based assessment of histological samples will occur at Screening and Weeks 36 and 64.

For testing of non-anal sites, vaginal, cervical (female subjects), penile (male subjects), and oropharyngeal (OP) samples (all subjects) will be obtained to characterize HPV infection at Day 0, and at Weeks 4,15, 28, 36, 64 and 88.

Safety Assessment: Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the Participant Diary Card (PCD).
2) All adverse events including SAEs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed to Week 88.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. Refer to Section 3.8 for stopping rule criteria.

Definition of Responder and Non-Responder:

Responder and non-responder definitions (**Table 2 through Table 7**) take into account both histopathologic regression of anal or anal/peri-anal HSIL **and** virologic (HPV-16/18) clearance as measured by intra-anal and/or peri-anal tissue, since HPV persistence is an important factor in the clinical progression of HSIL. Any case of histologically confirmed progression from HPV-16/18 positive anal or anal/peri-anal HSIL to carcinoma according to the PAC is considered a non-responder.

Table 2: Definition of Responder and Non-Responder for Composite Endpoint of Regression and Clearance

Responder	Non-Responder
No histologic evidence of anal or anal/peri-anal HSIL AND Negative PCR for HPV-16 or HPV-18 in anal lesion tissue AND No non-study treatment of curative intent of intra-anal and/or peri-anal lesions	Histologic evidence of anal or anal/peri-anal HSIL, anal Adenocarcinoma-in-situ (AIS), anal or anal/peri-anal carcinoma OR PCR positive for HPV-16 or HPV-18 in anal lesion tissue OR Any non-study treatment of curative intent of intra-anal and/or peri-anal lesions

Table 3: Definition of Responder and Non-responder for HSIL Regression Endpoint	
Responder	**Non-Responder**
No histologic evidence of anal or anal/peri-anal HSIL AND No non-study treatment of curative intent of intra-anal and/or peri-anal HSIL	Histologic evidence of anal or anal/peri-anal HSIL or carcinoma at evaluation OR Any non-study treatment of curative intent of intra-anal and/or peri-anal HSIL

Table 4: Definition of Responder and Non-responder for Viral Clearance Endpoint	
Responder	**Non-Responder**
No evidence of HPV-16 or HPV-18 in tissue/swab at evaluation AND No non-study treatment of curative intent of intra-anal and/or peri-anal HSIL	Evidence of HPV-16 or HPV-18 in tissue/swab at evaluation OR Any non-study treatment of curative intent of intra-anal and/or peri-anal HSIL

Table 5: Definition of Responder and Non-responder for Complete HSIL Regression Endpoint	
Responder	**Non-Responder**
No histologic evidence of anal or anal/peri-anal HSIL or LSIL AND No non-study treatment of curative intent of intra-anal and/or peri-anal HSIL	Histologic evidence of anal or anal/peri-anal LSIL, HSIL or anal or anal/peri-anal carcinoma at evaluation OR Any non-study treatment of curative intent of intra-anal and/or peri-anal HSIL

Table 6: Definition of Responder and Non-responder for Disease Non-Progression Endpoint

Responder	Non-Responder
No histologic evidence of a worsening anal or anal/peri-anal condition to anal or anal/peri-anal cancer relative to baseline AND No non-study treatment of curative intent of intra-anal and/or peri-anal HSIL	Histologic evidence of worsening of anal or anal/peri-anal condition to anal or anal/peri-anal cancer relative to baseline OR Any non-study treatment of curative intent of intra-anal and/or peri-anal HSIL

Table 7: Definition of Responder and Non Responder for Endpoint of Regression or Clearance

Responder	Non-Responder
No histologic evidence of anal or anal/peri-anal HSIL on histology OR No evidence of HPV-16 and/or HPV-18 intra-anal and/or peri-anal lesion tissue AND No non-study treatment of curative intent of intra-anal and/or peri-anal HSIL	Histologic evidence of anal or anal/peri-anal HSIL on histology AND Evidence of HPV-16/18 intra-anal and/or peri-anal lesion tissue OR Any non-study treatment of curative intent of intra-anal and/or peri-anal HSIL

Study Population:
Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2[a] within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16 and/or HPV-18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue (blocks only) provided to the Study Pathology Adjudication Committee (PAC) for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    a. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    a. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40mIU/mL;
    b. Surgically sterile due to absence of ovaries or due to bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    c. Subject agreement to avoid pregnancy for one month after last dose (Week 12 or Week 40);
    d. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of investigational product (Week 12 or Week 40). The following are acceptable methods:
        i. Hormonal contraception: either combined progestin-alone including oral contraceptive, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g. deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;
9. Men who would father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

[a] An HIV rapid test may be used given the following conditions are met: 1. The test is an antigen/antibody immunoassay, 2. The test is only done using blood, 3. The test must be performed in the office and done by qualified study staff members

Exclusion:

1. Untreated micro invasive cancer[a];
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN[b];
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN[b];
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN[b];
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN[b];
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;
8. Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
9. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
10. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
11. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator[c];
12. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;
    b. Any primary immunodeficiency;
    c. Long-term use (≥7 days) or oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, otic, nasal, topical, 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. Prior chemotherapy within 1 year;
    f. History of solid organ or bone marrow transplantation;
13. History of previous therapeutic HPV vaccination (however, licensed <u>prophylactic</u> HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
14. Receipt of any non-study related non-live vaccine within 2 weeks before or after any VGX-3100 dose;
15. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks before or after any VGX-3100 dose;
16. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
17. 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 the study results (e.g. chronic renal failure, angina, myocardial ischemia or infarctation, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias);

[a] This criterion includes subjects who have microscopic or gross evidence of invasive cancer, or the suspicion of cancer in any histopathologic specimen by any pathologist at screening.
[b] When observation is the standard of care this will not exclude a subject from the study.
[c] If the lab is redrawn and the result from the redrawn sample no longer meets this exclusion criteria, then the subject is not excluded on the basis of this criterion

18. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
19. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of Day 0;
20. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
21. 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;
22. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
23. Prior major surgery within 4 weeks of Day 0;
24. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent form (participating in an observational study is permitted);
25. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrillator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
26. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or evaluation of any study product;
27. Vulnerable Populations:
    a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;
    b. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
    c. Active military personnel;
    d. Study-related staff or family members of study-related staff

TRIAL SCHEDULE OF EVENTS

Table 8: Schedule of Events

Study Action	Screen (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Informed consent	X												
Medical History/Demographics	X												
Medications (prior/concomitant)	X	X		X		X	X	X	X	X		X	X
Socio-behavioral assessment	X								X			X[n]	X
Inclusion/Exclusion criteria[1]	X	X											
Physical exam (PE)/assessment [a]	X	X		X		X	X	X	X	X		X	X
Vital signs	X[b]	X		X		X	X	X	X	X		X	X
Screening safety (12 lead ECG, laboratories) [c]	X												
Pregnancy Testing [d]	X	X		X		X	X	X	X	X		X	X
HIV Ab by ELISA	X								X				
Blood immunologic samples	X[e]	X[e]					X[f]		X[e]				X[e]
Oropharyngeal (OP) rinse		X		X			X	X	X			X	X
Vaginal, cervical, and penile swab		X		X			X	X	X			X	X
Intra-anal and/or peri-anal swab	X	X		X			X	X	X			X	X
Digital Anal Rectal Examination DARE [g]	X	X		X			X	X	X			X	X
High Resolution Anoscopy (HRA) [h]	X	X		X			X	X	X			X	X
Lesion photography [i]	X	X		X			X	X	X			X	X
Biopsy [j]	X								X			X[q]	
Inject VGX-3100 +EP[k]		X		X		X				X[k]			
Post treatment reaction assessment		X		X		X				X			
Distribute Participant Diary Card (PDC)		X		X		X				X			
Review PDC [l]			X		X		X				X	X	
Patient Reported Outcomes (PROs) (SF-36v2™) (EQ-5D-5L)[m]		X[o]	X	X	X	X	X		X	X	X[p]	X	X

[1] Subject eligibility will be reconfirmed at every visit.

[a] Full Physical exam (PE) mandatory at Screening and study discharge (Week 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE.

[b] Screening vital signs must include a measured height and weight and calculated body mass index (BMI) (Bodyweight in kilograms divided by height in meters squared). Weight will be collected at all dosing visits.

[c] Screening 12-lead Electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, alanine aminotransferase (ALT), and Creatine Phosphokinase (CPK) performed within 45 days prior to first dose administration.

[d] Negative spot urine pregnancy test is required for female subjects at Screening, prior to each study treatment, high-resolution anoscopy (HRA), and biopsy/surgical excision; the pregnancy test at Week 40 would only be needed for subjects who receive an additional dose.

[e] At least 34 mL (4 x 8.5 mL yellow (ACD) tubes) whole blood and 4 mL serum per time point. At least 68 mL whole blood and 8 mL serum should be collected prior to first dose.

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

[g] Digital Anal Rectal Examinations (DARE) are to be performed once cytology has been collected and prior to HRA.

[h] An additional visit may be scheduled to perform HRA if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening) and Weeks 36 and 64 for Subgroup C unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the Pathology Adjudication Committee (PAC) for review.

[i] Photography of qualifying lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

[j] Tissue specimen (paraffin blocks) from all excised tissue lesion(s) that led to eligibility at study entry must be reviewed by the PAC and residual tissue from entry and Weeks 36 and 64 specimen(s) (paraffin blocks) must be sent to the central laboratory for immune analysis and Human Papillomavirus (HPV) testing.

[k] Potential dosing at Week 40 is applicable for partial responders only.

[l] A phone call will be used to review the Participant Diary Card (PDC) with subject within 8-14 days following doses 1 and 2. The subject will be expected to bring the PDC to the next visits for review. Subjects who receive an additional 4th dose will also have a phone call 8-14 days post dose 4 where the PDC will be reviewed. The subject should bring the PDC to the next visit.

[m] Patient-reported outcome (PRO) measures (SF-36v2™ andEQ-5D-5L, plus two additional "global" questions will be assessed as described in Section 6.13.

[n] This socio-behavioral assessment will only apply to those subjects in Subgroup C who receive a 4th dose of investigational product.

[o] PROs at this time point must be administered prior to first dose of study drug.

[p] PROs at this time point will only be for subjects who received a 4th dose of study drug.
[q] Under Protocol Amendment 3.0, in additional to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC.

1.0 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. Human Papillomavirus 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). In the United States (US), approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type (HR-HPV) and thus can cause cancer [2]. In U.S. adults through age 59 years, about 25% of men and 20% of women have genital HR-HPV infection [3]. Human Papillomavirus causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV Deoxyribonucleic Acid (DNA) was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (OP), 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS) [4]. An average of over 30,000 cases per year of HPV-attributable cancer were diagnosed during the period 2008 through 2012 in the U.S. [5]. Human Papillomavirus-16 and HPV-18 are the most significant among high-risk types since they are responsible for most HPV-caused cancers [4].

With regard to anal cancer, about 95% of cases are caused by HPV, and most of those cases are caused by HPV-16 [6, 7]; with some by HPV-18 and perhaps other HPV genotypes [2]. An estimated 8,300 new cases of anal cancer in the US are diagnosed each year (for year 2017), with an estimated 1,280 deaths annually due to this cancer [8]. In Canada, the latest available data is for year 2013, during which 580 new cases of anal cancer were diagnosed and 144 persons died due to anal cancer [9].

The precursor lesion to HPV-associated anal cancer historically was known as anal high-grade dysplasia or intraepithelial neoplasia. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term HSIL to encompass high grade dysplasia [10]. Among HPV-associated anal HSIL cases in the US, about 55% to 80% are associated with HPV-16/18, and worldwide about 80% of cases are associated with HPV-16/18 [7, 11, 12].

Left untreated, anal HSIL may progress to cancer. Spontaneous regression of these lesions may occur, but the available data indicate that such regression is in the minority of cases. For example, published results of a small observational study of anal HSIL in men who have sex with men (MSM) in Australia found spontaneous regression occurred in 29% of those HIV-negative after more than one year of follow-up time, with an even lower regression rate in those who were HIV-positive. That study also found that the majority (71%) of patients who regressed only did so to anal low-grade SIL (Low grade squamous intraepithelial lesion [LSIL]), with the remainder to normal tissue [13]. In an ongoing larger observational study of gay and bisexual men – the Study of the Prevention of Anal Cancer (SPANC) [14] -- also comprised of patients HIV-negative and HIV-positive (though with medically well-controlled CD4 cell counts), preliminary published data show that 55% of patients with anal HSIL, regardless of HIV status, had their HSIL persist to at least 12 months and HPV-16 was significantly associated with persistence as compared to other HPV genotypes (Relative Risk of 1.5) [15].

Spontaneous regression data from that study are not yet published, but preliminary data show spontaneous regression of only about 20% by one year of follow-up. Further, many of those patients who regressed later recurred to HSIL, suggesting that HSIL in some cases may be merely regressing to a level below the detection limit but is still present [16]. Other published data from a sub-study of that larger study indicate that HPV-16 E6-specific T-cell responses may be associated with recent anal HSIL regression (Pexact = 0.065) [17]. That finding provides further plausibility, in addition to other data summarized later in this protocol, that VGX-3100 plus electroporation treatment could cause anal HSIL regression.

Anal HPV infection spontaneous clearance in non-immunocompromised adults can occur, but such data are generally unavailable for persons who have anal HSIL. Nevertheless, high-risk HPV (HR-HPV) clearance by one year ranges from 56% to 78%, varying by gender and sexual preference etc., as found in large, prospective studies [18-20] with some wider variation in clearance rates for HPV-16 and HPV-18 specifically in those studies.

Collectively, the aforementioned anal HSIL regression and HPV clearance data comprise in part the historical control data that the results of the present trial will be compared to.

1.1.1 VGX-3100

VGX-3100 contains plasmids that target HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated Investigational Product (IP) designed as a non-surgical treatment of HPV-16/18-related anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, and PAIN3) via an immune response directed against HPV-16/18.

The initial formulation of VGX-3100 was Water for Injection (WFI) with 1% w/w poly-L-glutamate (WFI/LGS) that required frozen storage. This frozen formulation has been administered to more than 250 subjects in Phase 1 and 2 clinical trials. A buffered formulation of VGX-3100 was developed using a saline sodium citrate (SSC) solution, which is stored non-frozen (5°C). This non-frozen formulation of VGX-3100 was administered to 117 subjects in a Phase 1 clinical trial, HPV-101 in which subjects were randomized 1:1 to receive the non-frozen or frozen formulation of VGX-3100. In study HPV-101, healthy adults received three 6 mg IM doses of VGX-3100 in the frozen or non-frozen formulations followed by EP with the CELLECTRA™ 5Pdevice. The non-frozen formulation was found 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 enzyme-linked immunospot (ELIspot) assay.

Proof of concept was demonstrated in the prospective, randomized, double blind, placebo-controlled Phase 2b study of VGX-3100 (frozen formulation) followed by EP in the treatment of high grade cervical dysplasia, cervical HSIL associated with HPV-16/18 [1]. The Phase 2b study, HPV-003, enrolled 169 subjects with high grade cervical dysplasia from seven countries and one US Territory (Australia, Canada, Estonia, Republic of Georgia, India, South Africa, US and Puerto Rico). Subjects were randomized in a 3:1 ratio to treatment with VGX-3100 or placebo, respectively. All

subjects were to receive treatment on Day 0, Week 4 and Week 12. All subjects were to repeat cervical biopsy or Loop Electrical Excision Procedure (LEEP) of the cervix at Week 36 to assess efficacy defined as regression of high grade Cervical Intraepithelial Neoplasia (CIN) by histopathology. The primary endpoint was histopathologic regression of cervical lesions (CIN2 or CIN3) to Grade 1 Cervical Intraepithelial Neoplasia (CIN1) or less at the Week 36 visit. A secondary endpoint was clearance of HPV-16/18 in combination with histopathologic regression of cervical lesions to CIN1 or less. The proportions of subjects who met the primary and secondary endpoints were significantly higher in the VGX-3100 group vs. placebo in both per protocol (PP) and modified Intent to Treat (mITT) analyses. Robust T-cell activity was detected in VGX-3100 recipients compared to placebo recipients. VGX-3100 was generally safe and well tolerated when administered intramuscularly with electroporation.

1.1.2 ELECTROPORATION

CELLECTRA® 2000 & CELLECTRA™ 5PSP are both electroporation (EP) devices developed by INOVIO. Electroporation with CELLECTRA™5PSP 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 [21, 22]. EP is believed to increase the uptake and processing of plasmid DNA, thereby enabling increased expression and enhanced immunogenicity by 10 to 100 fold [23, 24]. 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 [21]. 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) [22, 23].

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 U.S. 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-16/18 related 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.

Inovio Pharmaceuticals Inc. device experience demonstrates that delivery of its proprietary electroporation pulses into muscle immediately following injection of DNA plasmids (including VGX-3100) is well-tolerated in humans and no significant safety issues have been identified [1, 22, 24]. For further information concerning the CELLECTRA™ 5PSP device please refer to the User Manual and the Investigator's Brochure.

1.1.3 DOSE RATIONALE

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

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 (AEs) from previous human studies with VGX-3100 and closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure, which were not clinically meaningful.

Based on the information above, the 6 mg dose was selected for study in HPV-003, Phase 2b study. The results obtained in the phase 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 2 trial [1].

1.2 POTENTIAL BENEFITS

Currently accepted surgical treatments are associated with a high recurrence rate, >50%. The current surgical approaches also have risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the anus. This study has been designed to provide non-surgical treatment with an aim of regression of the anal or anal/peri-anal HSIL and thus avoiding the need for surgical excision, infrared coagulation, electrocautery and laser therapy. In the absence of complete resolution of intra-anal and/or peri-anal lesions, there would still be potential benefit from a partial response, which would reduce or minimize the need for excisional or ablative treatment modalities. The other potential benefit is that the response to VGX-3100 is systemic and may clear the underlying HPV infection, which is the root cause. Consequently, there is the potential to reduce the risk of recurrence of anal or anal/peri-anal HSIL.

1.3 POTENTIAL RISKS

Risks associated with VGX-3100 for the treatment of anal or anal/peri-anal HSIL are injection site reactions related to the IM injection and/or electroporation. Based on the phase 1 and 2 clinical experience with VGX-3100 with healthy volunteers and in women with cervical HSIL, 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 anal dysplasia and possible missed diagnosis of an occult early invasive cancer for the VGX-3100 non-responders, who do not spontaneously regress. Although professional guidelines typically advocate excisional therapy for adults with HSIL, scientific data indicates that the rate of progression from pre-invasive to invasive cervical disease is slow, typically thought to take several years [10]. The risk of a missed diagnosis of an occult early invasive cancer exists for all current treatment modalities including surgical and ablative therapies. To mitigate these potential risks the study design includes numerous safeguards to detect disease progression or the presence of an undiagnosed occult

early invasive cancer. These include, careful selection of immunocompetent patients, thorough screening and baseline evaluation, frequent High-resolution anoscopy (HRA) and high-risk HPV testing throughout the trial. Investigators will be comprised of experienced physicians, who will have the discretion to obtain biopsies at any point if disease progression is suspected.

An independent Data and Safety Monitoring Board (DSMB) will also advise the Sponsor if it appears that the frequency of regression is unacceptably low. These measures should minimize the risk of progression of the HSIL and the risk of harboring an undiagnosed occult early invasive cancer.

In the HPV-003 study of women with cervical HSIL, 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 and even lower than the 6.7% that has been reported under standard of care settings [18].

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

2.0 PURPOSE AND HYPOTHESIS

2.1 PURPOSE

To provide a treatment to potentially regress and clear HPV-16/18 related anal or anal/peri-anal HSIL in individuals that are seronegative for HIV-1/2.

2.2 HYPOTHESIS

VGX-3100 followed by electroporation (EP) administered to adults with histologically confirmed anal or anal/peri-anal high-grade squamous intraepithelial lesions, HSIL, (AIN2, AIN3, PAIN2, PAIN3) associated with HPV-16/18 will result in a higher proportion with histopathologic regression of intra-anal and/or peri-anal HSIL lesions to no evidence of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or 18 than historical controls.

3.0 TRIAL DESIGN AND ENDPOINTS

HPV-203 is a Phase 2, open-label efficacy study of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18) administered by IM injection followed by EP in adult men and women who are HIV negative with histologically confirmed anal or anal/peri-anal HSIL associated with HPV-16 and/or 18. Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP. As shown in ***Figure 1***, study subjects will receive at least 3 doses of VGX-3100 depending upon their disposition with regard to histologic and lesion area changes during the trial. The first dose will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40. All subjects are scheduled to be followed to Week 88.

To be eligible for the study, subjects must consent to participate and agree to the collection of anal lesion tissue samples for anal cytology and genotyping, a Digital Anal Rectal Examination (DARE), blood samples for immunologic) assessments, HRA and

HRA guided biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening.

Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). Once the PAC confirms HSIL at Screening, the Week 36 and 64biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. In addition to HSIL lesions confirmed at Screening, all visible lesions should also have biopsy obtained at Week 64 and sent to central pathology lab for review by PAC. Subjects must also have intra-anal and/or peri-anal lesion tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be administered and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and additional PRO questions assessing quality of life after surgery or biopsy.

3.1 PRIMARY OBJECTIVE(S)

Determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16/18

3.2 PRIMARY ENDPOINT(S)

Proportion of subjects with no histologic evidence of anal or anal/peri-anal HSIL on histology (i.e., collected via biopsy or excisional treatment) and no evidence of HPV-16/18 at Week 36 from intra-anal and/or peri-anal lesion tissue

3.3 SECONDARY OBJECTIVE(S)

- Evaluate the **safety** and **tolerability** of VGX-3100 delivered IM followed by EP
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Determine the **efficacy** of three doses of VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue
- Determine the **efficacy** of three doses VGX-3100 as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal swab testing
- Determine the **efficacy** of three doses of VGX-3100 as measured by **complete histopathologic regression** of anal or anal/peri-anal HSIL to normal tissue
- Determine the **efficacy** of three doses of VGX-3100 as measured by **histopathologic non-progression** of anal or anal/peri-anal HSIL
- Describe the **efficacy** of VGX-3100 for **partial responders**, as measured by reduction in the number of intra-anal and/or peri-anal lesion(s), as applicable **and** the reduction in the size of peri-anal qualifying lesion(s), if present, **and** for whom the disease has not progressed according to Investigator judgment in subjects who did not have anal or anal/peri-anal HSIL lesion resolution at Week 36
- Determine the cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline

- Determine the **efficacy** of three doses of VGX-3100 with respect to histopathological regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18

3.4 ASSOCIATED SECONDARY ENDPOINT(S)

- Local and systemic events for 7 days following each dose as noted in the Participant Diary Card (PDC)
- **All** AEs including Serious Adverse Events (SAES), unanticipated (serious) adverse device effect (UADE), and other unexpected AEs for the duration of the study (through the Week 88 visit)
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (e.g. biopsies or excisional treatment) at Week 36
- Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal and/or peri-anal tissue by type specific HPV testing at Week 36
- Proportion of subjects with **no evidence** of HPV-16 and/or HPV-18 from intra-anal swab by specific HPV testing at the Weeks 36
- Proportion of subjects with **no evidence** of anal or anal/peri-anal LSIL or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, and PAIN3) on histology (i.e. biopsies or excisional treatment) at Week 36
- Proportion of subjects with **no progression** of anal or anal/peri-anal HSIL to carcinoma from baseline on histology (i.e. biopsies or excisional treatment) atWeek 36
- Percent **reduction** in the number of qualifying intra-anal and/or peri-anal lesion(s) and the size of peri-anal lesion(s) if present, as determined by the Investigator at Weeks 36, 64, and 88 compared to baseline.
- Flow Cytometry response magnitudes at baseline and Week 15
- Proportion of subjects with **no histologic evidence of anal or anal/peri-anal HSIL** on histology (i.e., collected via biopsy or excisional treatment) or **no evidence of HPV-16/18** at Week 36 from intra-anal and/or peri-anal lesion tissue

3.5 EXPLORATORY OBJECTIVE(S)

- Describe the long term **efficacy** of VGX-3100 with respect to combined **histopathologic regression** of anal or anal/peri-anal HSIL and **virologic clearance** of HPV-16 and/or HPV-18
- Describe the long term **efficacy** of VGX-3100, as measured by **histologic regression** of anal or anal/peri-anal HSIL
- Describe the long term **efficacy** of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18 by testing from lesion tissue
- Describe the long term **efficacy** of VGX-3100, as measured by **virologic clearance** of HPV-16 and/or HPV-18 by intra-anal swab testing

- Evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples
- Describe the **clearance** of HPV-16 and/or HPV-18 infection from non-anal anatomic locations
- Describe the association of microRNA (miRNA) profile, previous anoscopy, cytology and HPV testing results with Week 36 histologic regression
- Describe the patient reported outcomes (PRO) for subjects treated with VGX-3100
- Determine the humoral and cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline
- Determine the long term **efficacy** of VGX-3100 with respect to histopathologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18

3.6 ASSOCIATED EXPLORATORY ENDPOINT(S)

- Proportion of subjects with **no histologic evidence** of anal or anal/peri-anal HSIL on histology (i.e. collected via biopsy or excisional treatment) and **no evidence** of HPV-16 and/or HPV-18 at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
- Proportion of subjects with **no evidence** of anal or anal/peri-anal HSIL on histology (i.e. biopsies or excisional treatment) at Week 64
- Proportion of subjects with **no HPV-16 and/or HPV-18** at Week 64 by testing from intra-anal and/or peri-anal lesion tissue
- Proportion of subjects with **no evidence of HPV-16 and/or HPV-18** from intra-anal swab by specific HPV testing at Week 64 and Week 88Assessment of proinflammatory and immunosuppressive elements in tissue, where feasible.
- Proportion of subjects who have **cleared** HPV-16 and/or HPV-18 on specimens from non-anal anatomic locations as applicable based upon gender (i.e. oropharynx, cervical, vaginal, and penile at Week 36)
- HRA, cytology, and HPV test results and miRNA profile (baseline and at Weeks 15, 28, and 36) in conjunction with histologic regression of anal or anal/peri-anal HSIL at Week 36
- Patient reported outcome endpoints prior to first dose (Day 0), on the day of and following each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a 4^{th} dose.
- Levels of serum anti-HPV-16 and anti-HPV-18 antibody (Ab) concentrations at baseline and Weeks 15, 36, 64, 88 visits
- Interferon- γ ELISpot response magnitudes at baseline, and Weeks 15, 36, 64, and 88
- Proportion of subjects with **no histologic evidence of anal or anal/peri-anal HSIL** on histology (i.e., collected via biopsy **or** excisional treatment) or **no**

evidence of HPV-16 and/or HPV-18 at Week 64 from intra-anal and/or peri-anal lesion tissue

3.7 EFFICACY ASSESSMENT

Screening biopsies will be collected from all intra-anal and/or peri-anal lesions of adequate size (≥ 4mm). Visible lesions observed during HRA should be large enough to biopsy, but the biopsy (typically 4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study.

Given that HPV infection persistence is a critical factor in the clinical progression of HPV-associated anal or anal/peri-anal HSIL and also based upon the findings of the secondary objective of the HPV-003 CIN2/3 proof of concept study, the responder definition for the HPV-203 primary endpoint determination requires both histological regression of anal or anal/peri-anal HSIL and clearance of HPV-16 and HPV-18 [1].

Regression of anal or anal/peri-anal HSIL will be determined by histopathologic assessment of intra-anal and/or peri-anal tissue obtained from biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. In additional to HSIL lesion(s) found at Screening, all visible lesions will have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC. Tissue will be analyzed for evidence of histopathologic regression. Clearance of HPV-16/18 will be determined using the by type specific HPV polymerase chain reaction (PCR) test on intra-anal and/or peri-anal tissue performed at Screening and Weeks 36 and 64 when applicable.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0 (prior to dosing) and Weeks 4, 15, 28, 36, 64 and 88 as a less invasive measure for exploratory purposes to determine the presence of HPV-16 and/or -18 as well as other high risk HPV types using HPV testing. Similarly, vaginal, cervical (female subjects), penile (male subjects) and OP rinse samples (all subjects) will be obtained at Day 0 (prior to dosing), and at Weeks 4, 15, 28, 36, 64, and 88 to assess systemic virologic response to treatment.

If after evaluation of the biopsy tissue at Week 36, HSIL remains, but there is a reduction in intra-anal and/or peri-anal lesion(s) number and no increase in peri-anal lesion(s) size from baseline (Subgroup C, Figure 2), the Investigator will have the option to administer a 4th dose of VGX-3100 at Week 40 and the subject will continue on the study with HRA and biopsy at Week 64, i.e. the second efficacy checkpoint. Alternatively, the Investigator may choose to treat the subject with standard of care treatment (i.e. electrocautery, ablation, surgical excision), and the subject will continue on the study without further biopsy unless it is part of the standard of care. If HSIL remains based on the Week 64 biopsy results, the subject will receive standard of care and remain on the study for safety and follow up only. All tissue samples obtained from biopsies or removed per standard of care will be sent to the PAC for review.

3.8 SAFETY ASSESSMENT

Subjects will be monitored for:

1) Local and systemic events for 7 days following each VGX-3100 dose as noted in the PDC.

2) All AEs including SAEs, UADEs, and for the duration of the study.

All subjects will be followed for 88 weeks.

Data Safety & Monitoring Board (DSMB): An independent DSMB will meet quarterly to review safety data and tissue regression and viral clearance results. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis is planned. The following stopping rules will be applied:Stopping Rules (Criteria for Pausing of Study)

- If at any time during a study one-third (1/3) or more of the subjects experience an AESI, verified per protocol definition, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE), or death verified as related to study treatment occurs, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study, experience the same Grade 3 or 4 unexpected adverse event, verified per protocol definition and assessed as related to study treatment, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, verified per protocol definition and assessed as related to study treatment, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

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

Guidelines for assessing clinical abnormalities are in Section 7.0 in general and in **Table 11** provided in Section 6.1.2.

Guidelines for assessing relatedness are detailed in Section 7.7.

3.9 IMMUNOGENICITY ASSESSMENT

Cellular mediated immune responses in response to VGX-3100 treatment will be evaluated in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Week 15. Intra-anal and/or peri-anal tissue samples may also be analyzed for evidence of proinflammatory and immunosuppressive elements at Week 36 as compared to baseline (Screening), where feasible.

4.0 TRIAL POPULATION

4.1 INCLUSION CRITERIA

1. Must understand, agree and be able to comply with the requirements of the protocol and be able to provide voluntary consent to participate and sign an Informed Consent Form (ICF) prior to study-related activities;
2. Age 18 years and above;
3. Negative screening test for HIV-1/2[a] within 30 days of Dose 1;
4. Confirmed anal or anal/peri-anal HPV-16/18 infection at Screening by PCR from HSIL specimen;
5. Anal tissue (blocks only) provided to the Study PAC for diagnosis must be collected within 10 weeks of first dose of VGX-3100;
6. At least one anal or anal/peri-anal (AIN2/3 and/or PAIN2/PAIN3) lesion that is histologically-confirmed as HSIL by the PAC at Screening;
    i. The lesion needs to be large enough to biopsy, but the biopsy (≥4mm) should not remove the entire lesion in order to allow for continued lesion measurement while on the study;
7. Investigator judges the subject to be an appropriate candidate for histology collection procedures (i.e. excision or biopsy);
8. Female subjects, must meet one of the following criteria with respect to their reproductive capacity:
    i. Post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with follicle-stimulating hormone (FSH) level >40mIU/mL;
    ii. Surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to Screening;
    iii. Subject agreement to avoid pregnancy one month after last dose of IP (Week 12 or Week 40);
    iv. Women of Childbearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from Screening until one month following the last dose of IP (Week 12 or Week 40). The following are acceptable methods:
        1. 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);
        2. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        3. Intrauterine device or intrauterine system;

4. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject;

9. Men who could father a child must agree to use at least one form of birth control during or continued abstinence from heterosexual intercourse prior to the study, for the duration of study participation and one month after completion of VGX-3100 administration;
10. Normal Screening electrocardiogram (ECG) or Screening ECG with no clinically significant findings as judged by the Investigator

[a] An HIV rapid test may be used given the following conditions are met: 1. The test is an antigen/antibody immunoassay, 2. The test is only done using blood, 3. The test must be performed in the office and done by qualified study staff members

4.2 EXCLUSION CRITERIA

1. Untreated micro invasive or invasive cancer[a];
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN[b];
3. Biopsy-proven Vulvar Intraepithelial Neoplasia (VIN) and are not undergoing medical care and/or treatment for VIN[b];
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN[b];
5. Biopsy-proven Penile Intraepithelial Neoplasia (PIN) and are not undergoing medical care and/or treatment for PIN[b];
6. Anal or anal/peri-anal HSIL that is not accessible for sampling by biopsy instrument;
7. Intra-anal and/or peri-anal lesion(s) that cannot be fully visualized at Screening;8.Inability to have complete and satisfactory high resolution anoscopic exams (HRAs) as defined by full visualization of the anus, entire anal canal from the squamocolumnar junction at the border of the distal rectum, anal transformation zone, distal canal, anal verge, perianus;
8. Any treatment for anal or anal/peri-anal HSIL (e.g. surgery) within 4 weeks of Screening;
9. Pregnant, breast feeding or considering becoming pregnant within one month following the last dose of VGX-3100;
10. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 within 45 days prior to Day 0 or less than Grade 1 but deemed clinically significant by the Investigator[c];
11. Immunosuppression as a result of underlying illness or treatment including:
    a. Any prior history of other clinically significant immunosuppressive or clinically diagnosed Autoimmune disease;

b. Any primary immunodeficiency;

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, nasal, topical, 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 Tumor Necrosis Factor (TNF)-α inhibitors (e.g. infliximab, adalmumab or etanercept);

e. Prior chemotherapy within 1 year;

f. History of solid organ or bone marrow transplantation;

12. History of previous therapeutic HPV vaccination (however, licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
13. Receipt of any non-study related non-live vaccine within 2 weeks before or after any VGX-3100 dose;
14. Receipt of any non-study related live vaccine (e.g. measles vaccine) within 4 weeks before or after any VGX-3100 dose;
15. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treated as deemed by the Investigator;
16. 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);
17. Treatment for non-anogenital malignancy within 2 years of Screening, with the exception of superficial skin cancers that only require local excision;
18. Bleeding or clotting disorder or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) that would contraindicate IM injections within 2 weeks of a study dose;
19. History of seizures unless seizure free to 5 years with the use of one or fewer antiepileptic agents;
20. 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;
21. Resting heart rate <50 beats per minute (bpm) (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
22. Prior major surgery within 4 weeks of Day 0;
23. Participated in an interventional study with an investigational compound or device within 4 weeks of signing the ICF (participation in an observational study is permitted);
24. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;

a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;

b. Cardioverter-defibrilator or pacemaker on the ipsilateral side (to prevent a life-threatening arrhythmia) (unless deemed acceptable by a cardiologist);

c. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);

25. 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;

26. Vulnerable Populations:

a. Drug (i.e. prescription or illicit) or alcohol use or dependence that, in the opinion of the Investigator, would interfere with adherence to study requirements;

b. Prisoner or subject who is compulsorily detained (involuntary incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

c. Active military service personnel;

d. Study-related staff or family members of study-related staff

[a] This criterion includes subjects who have microscopic or gross evidence of invasive cancer, or the suspicion of cancer in any histopathologic specimen by any pathologist at screening.

[b] When observation is the standard of care this will not exclude a subject from the study.

[c] If the lab is redrawn and the result from the redrawn sample no longer meets this exclusion criteria, then the subject is not excluded on the basis of this criterion

4.3 DISCONTINUATION/WITHDRAWAL OF TRIAL SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION FROM THE STUDY

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from further treatment with VGX-3100. Subjects will not receive further doses of VGX-3100 followed by EP but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study.

If a subject manifests a Grade 3 toxicity attributable to VGX-3100/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM STUDY

Subjects who become ineligible to continue on the study based on no longer meeting the inclusion criteria should be discontinued from study treatment and managed per routine standard of care but should continue on the study without further biopsy.

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 anal or anal/peri-anal HSIL, and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls to the subject should be made and if that fails, then a certified letter is sent to the subject's last known mailing address) so that they can be considered withdrawn from the study for disposition purposes. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will the subject be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

If a subject elects to discontinue treatment/EP they should be encouraged to stay in the study and complete all follow-up visits and procedures and have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events (Table 8). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 88). A subject will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs and/or SAES present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 – Safety Parameters.

4.3.4 REASONS FOR DISCONTINUATION/WITHDRAWAL

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

- 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 AEs regardless of relation to study drug.
- Death of a subject, (including manner of death if known)
- Subject voluntarily withdrew consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it must be recorded on the eCRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Investigator decision to withdraw the subject from participation: Investigator determined a maternal obstetrical or medical need to withdraw subject. Investigator must consult the Medical Monitor before withdrawing a subject from participation in the study.
- Protocol Deviation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g. treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including 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 who receive study treatment and discontinue prior to Week 36, primary endpoint procedures, then supplementation of study subjects will be considered.

5.0 TRIAL TREATMENT

5.1 INVESTIGATIONAL BIOLOGIC PRODUCT

The IP to be used in this trial is described in **Table 9**. The IP will be presented in a clear glass cartridge and injected intramuscularly.

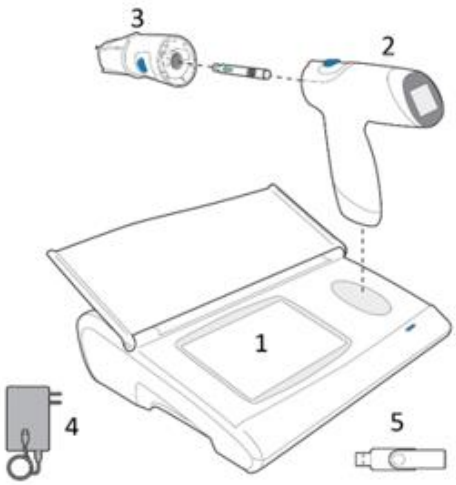
Table 9: Investigational Biologic Product

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

5.2 CELLECTRA™ 5PSP DEVICE DESCRIPTION:

VGX-3100 will be delivered using the CELLECTRA™5PSP device. The device consists of five (5) main components (see Figure 3).

Figure 3: CELLECTRA™ 5PSP Base Station with Handset



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

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

3) CELLECTRA™ 5PSP Sterile Single Use Array which consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) Drug Cartridge. The array accepts a standard, commercially available glass cartridge.

4) USB International Power Supply

5) Flash Drive

Base Station

The base station communicates instructions, alerts, and error messages to the user through a touch screen graphical user interface (GUI). It also accepts data inputs from the user, e.g., patient identification code, height, and weight; it communicates with the handset; provides energy access for the system through connection with standard wall electrical power supply sources (100-220V, ~0.5Amp, 50-60Hz); and serves as a docking and recharging station for the handset.

Handset

The handset facilitates delivery of the needles for injection and electroporation into the muscle tissue and executes the treatment sequence (drug injection, impedance check, and electroporation pulses). It has a display screen and speakers for user feedback and an embedded processor for running the system software that controls and measures all of the elements of the handset. The handset is powered by a custom, rechargeable battery pack that has its own safety circuit and is compliant to International Ethics Committee (IEC) 62133 and UL 2054. The handset is designed with three independent fail-safes to minimize the risk of electrical shock, short, or fire.

Array

The array is a single-use, sterile, disposable component constructed of commonly-used medical plastics and metals, with 5 fixed, stainless-steel electrodes (needles) and 1 IM injection needle. The needles are covered by a plastic shroud that retracts as the needles are inserted into the patient, then returns to the starting position as the needles are removed and locks out to prevent accidental needle sticks. The opposite end of the array accepts the drug cartridge, which is inserted cap-end-first until the bottom of the cartridge is flush with the opening of the array (indicated by an audible 'click'). When properly inserted, the septum is punctured and the cartridge cannot be removed. The 5PSP Array features no software.

The base station and handset with the 5PSP Array are illustrated in Figure 3).

Figure 3.

5.3 TREATMENT REGIMEN

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-203 study will receive the same three 6 mg doses of VGX-3100 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 at Week 12. A fourth dose may be administered at Week 40.

The first study treatment will be given as soon as possible following confirmation of anal or anal/peri-anal 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.

5.4 PACKAGING AND HANDLING

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

Table 10: Example of Packaging and Label Information

Cartridges (primary container)	**Pouches** (secondary packaging)
LABEL VGX-3100 Insert cap end Sponsor name IM administration Investigational Use Only	**LABEL BODY** Study ID VGX-3100 Single-use cartridge containing 1 mL IM administration via CELLECTRA™ 5PSP Store at 2-8°C, expiration date Caution Statement Sponsor name and address
	LABEL TEAR OFF Study ID VGX-3100 Patient ID: _____ Date: (DD-MMM-YYYY): _____ Must be used by (time): _____

See Figure 4 below for example of CELLECTRA™ 5PSP device component labels.

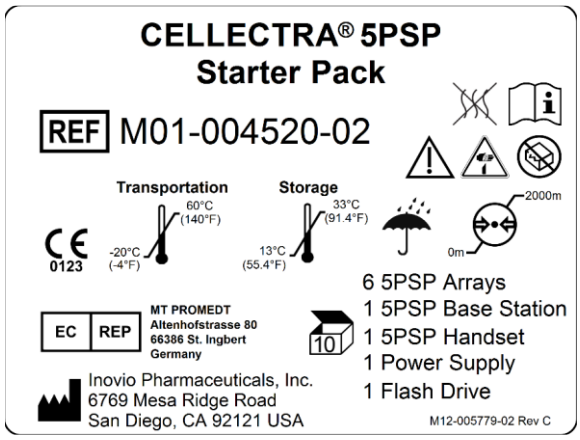
Figure 4: Examples of Device Labels (Base, Handset, Array, Outer Box)

Base Station Label

Handset Label

5PSP Array Label

Outer Box Packaging Label



5.5 HANDLING AND STORAGE OF IP AND DEVICE

The CELLECTRA™ 5PSP device and its components must be stored in a secure location according to the instructions in the User Manual. The CELLECTRA™ 5PSP device and its components must be stored between the temperature ranges 55.4°F-91.4°F and kept dry. The Sponsor should be notified of any deviations from this recommended storage condition. For the specific temperature guidelines for storing, please refer to the CELLECTRA™ 5PSP User Manual.

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.

5.6 PREPARATION AND DISPENSING

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. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. The Sponsor should be notified of any deviations from this recommended storage condition. Inovio Pharmaceuticals Inc. will be responsible for assuring the quality of the IP is adequate for the duration of the trial. Preparation and Dispensing

It is the responsibility of the Investigator to ensure that VGX-3100 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, remove the pouch from the refrigerator and allow to reach room temperature. The product cartridge must not be removed from the pouch until immediately prior to administration.

The pouch must not be discarded until:

1. Administration is completed and
2. All pertinent information from the pouch label has been documented in source.

The product must be used within 4 hours of removal from the refrigerator. If VGX-3100 is not used within this timeframe it must be discarded after reconciliation.

5.7 USE OF CELLECTRA™ 5PSP DEVICE

The instructions for use of the 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. Refer to the User Manual for further instruction. 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.

5.8 DRUG AND DEVICE ACCOUNTABILITY

5.8.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of IP 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;
- Date and initials of person responsible for each IP inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable

5.8.2 CELLECTRA™ 5PSP DEVICE ACCOUNTABILITY

The site is responsible for maintaining the device. The device must have full traceability from receipt of the products through the subject use, and the return of the device. The site must document acknowledgement of receipt and then notify INOVIO upon receipt of the device. This includes the content shipped and condition of the items upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 5PSP Base Station & Handset serial number, 5PSP 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.

5.9 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT AND CELLECTRA™ 5PSP DEVICE

5.9.1 RETURN OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be destroyed at the site per the institutions policy or returned to INOVIO or its designee, if the site cannot destroy the unused IP.

The used IP cartridge will be discarded along with the disposable array within a sharps container at site. Do not attempt to remove the cartridge from the array once it has been used.

It is the Investigator's responsibility to arrange for the 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 INOVIO personnel, StudyMonitor, or by the authorized site representative if the Study Monitor is not present

The unused IP can only be destroyed after being inspected and reconciled by the responsible INOVIO personal or designated Study Monitor.

If IP is returned to INOVIO, 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.

5.9.2 RETURN OF CELLECTRA™ 5PSP DEVICE

Upon completion or termination of the study, all investigational devices and unused components (Base, Station and Handset,) must be returned to INOVIO. Please contact an Inovio representative for specific instructions on the return of the device and components. Any unused or expired 5PSP Arrays should be destroyed on site per the site’s institutional policy. If a site’s policy does not allow for the destruction of the Arrays on site, please contact an Inovio representative for further instruction.

All device components returned to INOVIO 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.

If any component is to be 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, 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.

6.0 TRIAL 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.

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

Protocol waivers or exemptions will not be granted. 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 are essential and required for study conduct. Subject eligibility should be reconfirmed at every study visit.

6.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial subjects, explain the trial, and provide them with an ICF that describes the Screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial 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 trial 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.

6.2 BEFORE TREATMENT PROCEDURES

Subjects who consent to participate must have paraffin-embedded tissue block(s) from a previous biopsy (ies) and/or newly collected intra-anal and/or peri-anal biopsy tissue samples (formalin fixed tissue) sent to the central pathology lab for review by the 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), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with anal or anal/peri-anal HSIL, by a local pathologist, where the initial biopsy tissue obtained as part of standard of care are not available or cannot be obtained within a reasonable timeframe, biopsy samples should be collected from all intra-anal and/or peri-anal lesions of adequate size during Screening following the consent of the subject. The 10 week Screening window begins upon collection of the biopsy sample(s) that will be evaluated by the PAC.

At Screening, subjects must have a diagnosis of histologic anal or anal/peri-anal HSIL confirmed by the PAC and intra-anal and/or peri-anal specimen test positive for HPV-16/18 by PCR to be eligible for participation in the study (provided the subject also meets other eligibility criteria). Subjects whose intra-anal and/or peri-anal specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16/18.

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

6.2.1 SCREENING EVALUATIONS

The following evaluations/actions, unless noted, will be performed within 10 weeks and up to Day 0 – except for the HIV test which must be performed within 30 days prior to Day 0 and the safety laboratory collections/assessments and ECG, which must be performed within 45 days prior to Day 0. All Screening assessment values must be reviewed ***prior*** to study treatment. Some of these evaluations/actions will be performed again later in the trial (see later text and the Schedule of Events (**Table 8**) for more detail).

- Signed ICF
- Medical history/demographics, including history of prior anal or anal/peri-anal HSIL
- Socio-Behavioral Assessment; including smoking history, exposure to second-hand smoke, alcohol intake history, recreational drug use and contraceptive use
- Prior concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Complete Physical Examination
- Vital signs (including oral temperature, respiratory rate, blood pressure and heart rate), height, weight and body mass index (BMI) measurements
- 12-lead ECG (within 45 days prior to Day 0)
- Baseline laboratory evaluations (including complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine (Cr), glucose, alanine aminotransferase [ALT], and creatine phosphokinase [CPK]) (to be performed within 45 days prior to Day 0)
- Urine pregnancy test
- Serology (HIV Ab) within 30 days prior to Day 0
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- Digital Anal Rectal Examination (DARE)
- Lesion photography (intra-anal and/or peri-anal)
- High Resolution Anoscopy (HRA) with Biopsy (tissue must be reviewed by the PAC).
    - If a historical biopsy is used with a corresponding HRA evaluation, then the HRA does not need to be repeated for Screening to determine eligibility as long as it is within the allowable window of 10 weeks.
- Whole blood (at least 68 mL) and serum (at least 8 mL) for baseline immunology including miRNA profile must be collected **before** dosing on Day 0
    - It is acceptable to collect the blood as follows:
        - Screening: obtain 34 ml of whole blood and 4 ml of serum

- Day 0: obtain 34 ml of whole blood and 4 ml of serum **prior** to dosing

6.3 DURING TREATMENT PROCEDURES BY VISIT

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

6.3.1 DAY 0

The following study evaluations will be performed at Day 0 (unless noted) *prior* to the first study treatment:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA profile (if whole blood and serum were not collected at Screening, then 68 ml of whole blood and 8 ml of serum should be drawn at this time point **prior** to dosing)
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcome (SF-36v2™ and EQ-5D-5L) (may be performed at Day -1 or on Day 0, again provided it is done **prior** to the first study treatment)
- Study treatment administration

The following evaluations will be performed on Day 0 after study treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute Participant Diary Card (PDC)

****Please remember to download EP data from the CELLECTRA™5PSP device following each study treatment.****

6.3.2 8-14 DAYS POST DOSE 1 PHONE CALL

The following information will be evaluated during the phone call:

- Review Day 0 of 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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.3 WEEK 4 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant mediation review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (the subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Collect and review PDC for dose 1
- Study treatment administration

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

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

Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

****Please remember to download EP data from the CELLECTRA™ 5PSP device following each study treatment.****

6.3.4 8-14 DAYS POST DOSE 2 PHONE CALL

The following information will be evaluated during the phone call:

- Review of PDC for dose 2 (after reviewing the PDC and post treatment injection assessment with the subject on the phone, the Investigator or study personnel will determine whether an office visit is needed for further evaluation)

- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.5 WEEK 12 (± 4 DAYS)

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

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Collect and review PDC for dose 2
- Study treatment administration

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

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

****Please remember to download EP data from the CELLECTRA™5PSP device following each study treatment.****

6.3.6 WEEK 15 (± 1 WEEK)

The following study evaluations will be performed at Week 15:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunology including miRNA
    - 51 ml of whole blood and 4 ml serum should be drawn at this time point
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA

- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.7 WEEK 28 (± 1 WEEK)

The following study evaluations will be performed at Week 28:

- Reconfirm subject eligibility
- Concomitant medical review
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical, and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)

6.3.8 WEEK 36 (± 1 WEEK)

The following study evaluations will be performed at Week 36:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA

- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.9 WEEK 40 (± 1 WEEK)

The following study evaluations will be performed at Week 40:

- Reconfirm subject eligibility
- Concomitant medication review
- Targeted Physical assessment
- Vital signs including weight
- Urine pregnancy test
- Study treatment administration
- Based on biopsy results collected at Week 36 and Investigator judgment, a 4th dose may be given at this visit

****Please remember to download EP data from the CELLECTRA™ 5PSP device following each study treatment. .****

The following study evaluations will be performed at the Week 40 post treatment:

- Post treatment AEs and injection site reaction assessment at least 30 minutes after study treatment
- Distribute PDC
- Patient reported outcomes:- the two "global" questions and SF-36v2™ and EQ-5D-5L

6.3.10 8-14 DAYS POST DOSE 4 PHONE CALL (FOR SUBJECTS WHO RECEIVED A 4TH DOSE)

The following information will be evaluated during the phone call:

- Review PDC for dose 4 (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)
- Remind subject to self-complete the PRO questionnaires (SF-36v2™ and EQ-5D-5L)

6.3.11 WEEK 64 (± 2 WEEKS)

The following study evaluations will be performed at Week 64:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment (only for subjects who received a 4th dose at Week 40)

- Targeted Physical assessment
- Vital signs
- Urine pregnancy test
- Oropharyngeal rinse
- Vaginal, cervical and penile swab
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Biopsy (paraffin blocks)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.3.12 WEEK 88 (± 2 WEEKS)

The following study evaluations will be performed at Week 88:

- Reconfirm subject eligibility
- Concomitant medication review
- Socio-behavioral assessment
- Full Physical assessment
- Urine pregnancy test
- Vital signs
- Whole blood and serum for immunology including miRNA profile
- Oropharyngeal rinse
- Vaginal, cervical, and penile swabs
- Intra-anal and/or peri-anal swab (subject should be requested to abstain from any sexual activity and refrain from the use of douching or vaginal and anal lubricants/medication for a period of 24 hours prior to sample collection)
- DARE
- HRA
- Lesion photography (intra-anal and/or peri-anal)
- Patient reported outcomes (SF-36v2™ and EQ-5D-5L)

6.4 TRIAL PROCEDURES

6.5 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all trial-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., ANUS01001). 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.

6.6 DEMOGRAPHICS

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

- Age
- Gender
- Race/ethnicity
- Dominant hand/arm

6.7 SAFETY EVALUATIONS

6.7.1 PHYSICAL EXAM

A full Physical exam (PE) will be conducted during Screening and study discharge (Week 88). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems, and a DARE. All assessments not completed should be marked as not done.

A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

6.7.2 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 prior to measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.7.3 HEIGHT AND WEIGHT

Weight and height will be collected at all dosing visits in order to calculate the BMI.

6.7.4 MEDICAL HISTORY

Medical history, including history of prior anal or anal/peri-anal dysplasia and gynecologic history will be obtained at Screening. For females, previous history of treatment for VIN, CIN and/or VAIN will be collected. All relevant past and present conditions, as well as prior surgical procedures at least 6 months prior to enrollment will be recorded for the main body systems.

6.7.5 SOCIO-BEHAVIORAL ASSESSMENTS

Socio-Behavioral Assessment, including self-reporting of the following: smoking history, history of exposure to second-hand smoke, alcohol intake history, recreational drug use history, history of contraceptive use and type of contraceptive if known, reproductive history, sexual preference and sexual practices history, and pregnancy history will be obtained at Screening.

At Weeks 36, 64 (only for subjects who receive a 4th dose), and 88, a socio-behavioral assessment will be performed to document any changes from Screening and/or other time periods.

6.7.6 LABORATORY EVALUATIONS

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

Complete Blood Count:

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

Serum Chemistry:

- Glucose
- Blood urea nitrogen
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase

6.7.7 PREGNANCY TESTING

For women of reproductive potential, a negative spot urine pregnancy test is required at Screening, and prior to each study treatment, HRA, DARE and surgical excision or biopsy.

6.7.8 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.

6.7.9 PARTICIPANT DIARY CARD (PDC)

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 11:59pm)
- 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 days post dose phone calls and at the next in-person visits.

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 criteria for a Grade 1 or higher AEs should be documented as an AE 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.

6.8 INJECTION AND ELECTROPORATION (EP)

Subjects will receive at least three doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by IM injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 5PSP. A fourth dose is optional for those assessed to be partial responders at the Week 36 efficacy assessment. Study treatment plus EP must not be given within 2 cm of a tattoo, keloid or hypertrophic scar, or if there is implanted metal within the same limb. EP may not be performed in the same arm adjacent to an implantable medical device (e.g., cardiac pacemaker, defibrillator or retained leads following device removal). The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, and at Week 40 (for Subgroup C, Figure 2 only). Please refer to the Investigator's Brochure for further information.

6.9 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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, and Weeks 4 and/or Week 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.

6.10 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 into the study as listed in the Schedule of Events (**Table 8**).

6.11 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

The injection site will be assessed by study personnel prior to and between 30-45 minutes after each study treatment. Subjects will be advised to record local and systemic AEs for 7 days after each study treatment on a PDC which will be reviewed with study personnel 8 – 14 days after doses 1 and 2, Week 15, and 8-14 days after dose 4 (if applicable).

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any AEs, 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 AEs will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's Case Report Form (CRF).

6.12 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 11**.

Table 11: Grading Scale for Injection Site Reactions

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

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

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

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

***Sponsor defines daily activity as impact lasting ≥ 24 hours

6.13 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, PRO instruments will be administered. The following PRO questionnaires will be used:

- **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [25]. SF-36v2™ will be administered at the following time points:
  - Day 0 (***before*** the first study treatment)
  - 8-14 days post dose 1
  - Week 4 (post dose 2)
  - 8-14 days post dose 2
  - Weeks 12 (post dose 3), 15, 36, 40
  - 8-14 days post dose 4* (only for those who received a 4th dose)
  - Weeks 64, 88
- **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [26, 27] and will be administered as described below:
  - Day 0 (***before*** the first study treatment)
  - 8-14 days post dose 1
  - Week 4 (post dose 2)
  - 8-14 days post dose 2
  - Weeks 12 (post dose 3), 15, 36, 40
  - 8-14 days post dose 4* (only for those who received a 4th dose)
  - Weeks 64, 88

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

- **Additional Global PRO Questions-** regarding quality of life after surgery or biopsy. These two questions will be administered at Week 40 only.

6.14 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

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

A standardized binding enzyme-linked immunosorbent assay (ELISA) may be performed to measure the anti–HPV-16/18 Ab response induced by VGX-3100.

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

Additional assessment of cellular immune activity will occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4,

CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

6.15 PROFILING OF MIRNA

Profiling of miRNA may occur via the use of either sera or plasma obtained at Screening, Day 0 and Weeks 15 and 36. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 samples may be done as a comparison against Day 0 in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun to explore construction of an algorithm to predict treatment success with VGX-3100.

6.16 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then the relevant paraffin blocks may be collected for the assessment of proinflammatory and immunosuppressive elements. . Assessment of markers may include, but are not limited to, CD8+ and FoxP3+ infiltrating cells as well as Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.17 ANAL AND/OR PERI-ANAL HPV TESTING

All intra-anal and/or peri-anal lesions of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL sites(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. In addition to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC. Intra-anal and/or peri-anal swabs will undergo HPV testing using a PCR based assay, SPF10.

The subject will be requested to abstain from sexual activity and refrain from the use of douching to eliminate potential interference with the results of HPV testing.

Intra-anal and/or peri-anal swabs will be obtained at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 in ThinPrep™ collection media. The HPV Cobas test will be performed on the ThinPrep™ specimens at Screening, and Weeks 36 and 64 when applicable. Anal cytology will be performed on intra-anal samples. At each of these visits, a recent history will be collected via self-report.

6.18 HPV TESTING FROM OTHER ANATOMICAL SITE (NON-ANAL)

Vaginal, cervical (female subjects), penile (male subjects), and OP rinse samples (all subjects) will be obtained at Day 0, and Weeks 4, 15, 28, 36, 64, and 88 to assess virologic clearance at non-anal sites using a PCR based HPV assay. All samples will be read in a central laboratory.

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

6.19 ANAL PHOTOGRAPHS AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of anal or anal/peri-anal HSIL confirmed by the PAC at Screening. Subjects will undergo HRA at Screening, Day 0, and at Weeks 4, 15, 28, 36, 64, and 88 to identify all intra-anal lesion(s). All intra-anal and/or peri-anal lesion(s) of adequate size (≥4 mm) will be biopsied at Screening. Once the PAC confirms HSIL at Screening, the Week 36 and 64 biopsies will be obtained from all HSIL site(s) confirmed by the PAC at Screening, unless the Investigator suspects disease progression. Investigators should follow **Table 1**: Minimally Required Procedure at each Biopsy Visit for the Weeks 36 and 64 biopsies. Under the Protocol 3.0 Amendment, in additional to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC. Photography of all qualifying intra-anal and/or peri-anal lesion(s) must be performed prior to and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.

If the intra-anal and/or peri-anal tissue sample(s) result suggests progression to cancer, the Investigator may schedule an ad hoc visit to perform HRA and possible biopsy if clinically indicated.

6.20 UNSCHEDULED BIOPSIES

Unscheduled biopsies may be performed on new lesions or suspected progression of original lesions per the Investigator's medical judgment during the study. 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. All biopsy samples/excised tissue (including standard of care) will be sent to the central pathology lab for review by the PAC.

6.21 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 eCRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to the 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 eCRFs. 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 eCRF.

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, nasal, topical, 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.

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.

6.22 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, including illicit drugs, taken to the Investigator and/or other study personnel. To remain in the study, illicit drugs should not be taken.

Subjects should refrain from becoming pregnant until one month following the last dose of IP (Week 12 or Week 40) by using appropriate contraceptive measures (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

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

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

As a requirement for inclusion in the HPV-203 study, Investigators will only be chosen if they are experienced in the management of anal cancer, and are experienced in performing HRA.

HPV-203 Investigators are instructed to perform additional, ad hoc HRA exams and biopsies if they suspect potential disease progression. Subjects that undergo an unscheduled biopsy will be classified as a non-responder in the efficacy analyses. These additional measures should minimize the risk of progression of anal or anal/peri-anal HSIL and the risk of harboring an undiagnosed occult early invasive anal or anal/peri-anal cancer. The frequency of close monitoring by experienced Investigators should minimize the risk of cancer progression during the study and the additional measures are beyond what is expected in standard of care.

7.2 ADVERSE EVENTS (AEs)

An 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 AEs 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 eCRF, including the event's seriousness, severity, action taken, and relationship to IP. Adverse Events should be followed until resolution or stable and the outcome will be documented on the appropriate eCRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

Adverse Events 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 increased 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 demise, still birth, congenital anomaly of fetus/newborn);
- AEs that occur from the study Screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE;
- Conditions that lead to a medical or surgical procedure.

Adverse Events do not include the following:

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

7.3 SERIOUS ADVERSE EVENTS

A SAE is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;

- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an Emergency room (ER) or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, or 3) the development of drug dependency or drug abuse.

Classification of Serious Adverse Events:

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

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.15.

7.4 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose; for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the AEs. An AE 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 ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of serious expected AEs, 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

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 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 eCRF at the maximum severity reported.

The Investigator will grade laboratory AEs and clinical AEs or SAEs with respect to the following levels of severity as per CTCAE v 4.03 for applicable patient populations:

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

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

7.7 CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable causal relationship to the administration to either or both IP and/or the CELLECTRA™ 5PSP device. The

Investigator will assess causal relationship of the AE separately to each of the investigational drugs and also the investigational device. The reasonable causal relationship means that there are facts (evidence) or arguments to suggest a causal relationship. An AE may also be assessed as not related to either or both IP and/or investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs 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 AE 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 VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation or deemed clinically significant by the Investigator must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, and 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 Sections 7.2 and 7.3. 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 is assessed as detailed in Section 7.6.

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT).

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines not only the severity of the event but also whether the abnormality in question is "clinically significant (CS)" or "NCS." CTCAE v. 4.03 grading criteria can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.9 POST-TRIAL 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 probably or possibly related to the study treatment, he/she should promptly document and report the event to the Sponsor.

7.10 PROCEDURES FOR DOCUMENTING PREGNANCY DURING THE TRIAL

Should a subject become pregnant after enrolling in the study, she will not be given any further treatments with the IP. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor or its designee by fax or email, as described in Section 7.15. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further 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 Sponsor.

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.11 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 88.

The sources of AEs cover:

1. The subject's response to questions about his/her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate eCRF.

Any SAE occurring during the course of the study must be reported to the Sponsor within 24 hours of awareness.

7.12 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 AEs classified by system organ class (SOC), preferred term, severity, and relationship to study treatment;
- Changes in safety laboratory parameters (e.g., hematology and serum chemistry);
- 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.

7.12.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

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

As per the Toxicity Grade for Healthy Adults, the most severe grade for that particular event is to be documented in the eCRFs.

Sites will inform the Sponsor via method described in Section 7.15 within 24 hours to discuss whether further dosing for the particular subject should continue.

7.13 ADVERSE EVENT REPORTING

To assure the safety of the participants, information about all AEs (see Section 7.2), whether volunteered by the subject, discovered by the 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.

7.14 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited AEs will be collected throughout the study and recorded in the Electronic Data Capture (EDC) system. The Study Report will analyze and summarize all AEs throughout the study. Emphasis will be placed on the following:

1. Certain AEs of interest will be solicited during the 7 days following each administration of Study Treatment and summarized separately
2. Unsolicited AEs will be collected and summarized for the entire study period

7.15 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS AND AESIS

The reporting period for SAEs (without regard to causality or relationship) and AESIs is comprised of the period following the signing of the ICF through Week 88. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator will complete the SAE/AESI Report form and report the event to the Sponsor within 24 hours of becoming aware of the event. The Investigator may also directly report this event to the IRB/EC according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.5 (UADE) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant 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.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor or its designee. If the Investigator becomes aware of an SAE in a study subject after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the Investigator will report it to the Sponsor or the appropriate designee.

SPONSOR CONTACT INFORMATION

MEDICAL MONITOR: [redacted], M.D., Ph. D.
EMAIL: [redacted]

SAE REPORTING INFORMATION

EMAIL: safety.inovio@apcerls.com
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is an attachment to an e-mail message, to the email address as indicated above. Any SAE supporting documents provided by facsimile (Fax) are to include a coversheet that identifies the reporter name and contact information of the study site.

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.

In addition to providing the SAE report to the Sponsor or designee within 24 hours of becoming aware of the event, the AE that is serious must be recorded in the AEs eCRF. The entry into the eCRF is required to be done as soon as possible.

The Investigator will supply the Sponsor and the IRB/EC with more information as it becomes available and any additional requested information. The original SAE form must be kept at the study site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

When recording the SAE form, correct medical terminology/concepts are to be used and the use of abbreviations and colloquialisms are to be avoided.

Serious Adverse Events 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.

In the event of a pregnancy, the Investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

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 experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.4 and 7.16).

7.17 REPORTING OF CELLECTRA™5PSP DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported within 24 hours of becoming aware of the event per Sections 7.2 and 7.3.

Any problems experienced including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form provided must be completed and emailed to the Sponsor at clinicalcomplaint@inovio.com.

Additional instructions on complaint reporting to be provided separately.

7.18 TRIAL DISCONTINUATION

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

Should the trial be terminated and/or the site closed for any reason, all investigational drugs & devices must be returned to INOVIO or its representative. The PI should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 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 or its representative.

This is a single-arm, multi-center, open-label clinical trial of VGX-3100 in subjects with a diagnosis of AIN2, AIN3, PAIN2, or PAIN3 associated with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of AIN/PAIN HSIL and viral clearance of HPV-16/18 based on tissue collected at Week 36. The primary hypothesis is that the treatment will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16/18 infection, complete regression, non-progression, and anatomic extent. Other secondary analyses concern safety and cellular immunological measures. Exploratory efficacy analyses concern extended dosing with respect to regression, clearance, clearance among non-anal anatomic locations, and association of miRNA profile, anoscopy, cytology, and virology with efficacy. Other exploratory analyses pertain to humoral and cellular immunological measures, tissue immunological measures, and PRO.

8.3 STATISTICAL HYPOTHESES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations are:

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSES

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint. The primary hypothesis of superiority is: H0: $p \leq 0.15$ vs. H1: $p > 0.15$.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.05 and the corresponding lower bound of the one-sided 95% CI exceeds 0.15.

For the analysis, the efficacy time frame is defined by any time starting from 14 days prior to the specified visit week.

The endpoint will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions.

8.5.2 SECONDARY ANALYSES

The secondary efficacy binary endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values. The efficacy time frame is defined in the same manner as for the primary endpoint. All of the efficacy binary endpoints will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions.

The anatomic extent endpoint will be analyzed by calculating the mean percent change in surface area and the mean percent change in number of lesions and associated 95% t-distribution based confidence intervals.

Post-baseline increases in Flow responses will be summarized with medians and 95% CIs. Valid samples for statistical analysis purposes will be those collected within 14 days of the specified visits. Baseline is defined as the last measurement prior to the first treatment administration.

8.5.3 SAFETY ANALYSES

All AEs will be summarized among the safety population by frequency. These frequencies will be presented overall and separately by dose, and will depict overall, by SOC 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 AE data will be based on events occurring within 28 days following any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days following any dose and regardless of when they occurred.

8.5.4 DISPOSITION

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

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables for the mITT population.

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

Prior medications are those that were used and stopped 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. Data for all prior medications will be summarized with percentages for the mITT population.

8.5.6 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 will not be adjusted for possible early stopping due to futility.

8.5.7 MULTIPLICITY

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

8.5.8 MISSING VALUES

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.

No other missing data will be imputed or replaced.

8.5.9 EXPLORATORY ANALYSES

The exploratory efficacy binary endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values. The efficacy time frame is defined in the same manner as for the primary endpoint. All of the efficacy binary endpoints will be analyzed in two ways: a) based on all lesions and b) based on qualifying and new lesions. Also, the Week 64/88 binary endpoints will be analyzed a) overall and b) according to three or four doses received.

Other analyses will examine the relationship between the primary efficacy endpoint and a) miRNA results, b) HRA results, c) cytology results, and d) HPV results. Relationships will be examined with contingency tables and/or logistic regression models which model the primary endpoint versus these results as regressor variables.

Post-baseline ELISA titers will be summarized with geometric means and associated t-distribution based 95% CIs. Post-baseline increases in ELISPOT will be summarized with medians and 95% CIs.

The change in tissue immune response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.6 SAMPLE SIZE/POWER

A sample of 24 subjects provides ~80% power to declare superiority over historical control, assuming the true proportion of subjects who achieve the primary endpoint is 40% for the treatment arm versus 15% for the historical control, and that 90% are evaluable at Week 36 from 1st dose.

8.7 RANDOMIZATION AND BLINDING

This is an open-label trial, and therefore, site personnel, individual subjects and INOVIO or its representative trial personnel will be aware of the treatment allocations for this trial. Randomization does not apply.

9.0 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical trial 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

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., ICF, 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:

- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of trial-related information (refer to trial files) that include all correspondence with the IRB/EC.
- Notify the IRB/EC when the trial is completed (i.e. after the last visit of the final trial subject).
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.

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 OFFICE OF BIOTECHNOLOGY ACTIVITIES

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 [NIH] Office of Biotechnology Activities [OBA]) governing research that involves recombinant or synthetic nucleic acid.

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 trial, 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 (Section 6.1).

9.5.2 COMPLIANCE WITH IRB/EC REQUIREMENTS

This trial 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 trial 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.

9.5.4 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURE REGULATIONS (21CRF PART 11)

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

9.5.5 COMPLIANCE WITH PROTOCOL

Subjects will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviation (PD), should a deviation be discovered, Sponsor must be informed immediately. Any PD 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 prior review and documented approval/favorable opinion from the Sponsor and IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects. While every effort should be made to avoid PD, should a

deviation be discovered, Sponsor must be informed immediately. Any PD impacting Subject safety must be reported to the Medical Monitor immediately.

10.0 DATA COLLECTION, MONITORING, AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial 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 trial Sponsor, the governing health authorities or the FDA, if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

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

Information about trial subjects will be kept confidential and managed in accordance with the requirements of the HIPAA of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

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

11.0 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 trial.

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.

Case Report Form will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified with an SID.

It is the Investigator's responsibility to retain trial essential documents for at least two (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 two (2) years have elapsed since the formal discontinuation of clinical development of the IP. 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.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY AND QUALITY MONITORING

An independent 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 there appears to be a regression with VGX-3100.However, no formal interim analysis will be performed.

12.2 PATHOLOGY ADJUDICATION COMMITTEE

All anal biopsies will be read by a central expert PAC to ensure consistent assignment of disease status for both study eligibility and the efficacy analysis. The PAC will consist of a total of four pathologists in separate locations. Each specimen will be read by two pathologists independently in a blinded fashion. The logistics and details of the PAC are detailed in the PAC Charter.

12.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:

- Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
- Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities continue to be acceptable.
- Compare the trial eCRFs 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.

13.0 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 at least 60 days prior to submission for publication. The Sponsor will have 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) will 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 US Patent and Trademark Office and/or foreign patent office(s).

14.0 LIST OF ABBREVIATIONS

Ab	Antibody
ADR	Adverse Drug Reaction
AEs	Adverse events
AESI	Adverse Event of Special Interest
AIN	Anal Intraepithelial Neoplasia
AIS	Adenocarcinoma-in-situ
ALT	Alanine Aminotransferase

BMI	Body Mass Index
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIN	Cervical Intraepithelial Neoplasia
CIN1	Grade 1 Cervical Intraepithelial Neoplasia
CIOMS-I	Council for International Organizations of Medical Sciences
Cr	Creatinine
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CPK	Creatine Phosphokinase
DARE	Digital Anal Rectal Examination
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
ELIspot	Enzyme-linked Immunospot Assay
EP	Electroporation with CELLECTRA™5PSP
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ER	Emergency Room
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
gbm	gay and bisexual men
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HRA	High-resolution Anoscopy
HR-HPV	High-risk HPV Type
HSIL	High Grade Squamous Intraepithelial Lesion
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug
INOVIO	Inovio Pharmaceuticals, Inc.
IP	Investigational Product
IRB	Institutional Review Board
IRB/IEC	Institutional Review Board or Independent Ethics Committee
ISO	International Organization for Standardization
LAST	Lower Anogenital Squamous Terminology
LSIL	Low Grade Squamous Intraepithelial Lesion
miRNA	MicroRNA
mITT	Modified Intent to Treat
MSM	men who have sex with men

NCS	Not Clinically Significant
OBA	Office of Biotechnology Activities
OP	Ororpharyngeal
PAIN	Peri-anal Intraepithelial Neoplasia
PAM	Protocol Administrative Memo or Letter
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIN	Penile Intraepithelial Neoplasia
PP	Per Protocol
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PDC	Participant Diary Card
PE	Physical Exam
PRO	Patient-reported Outcome
SAEs	Serious Adverse Events
SF-36v2™	36-Item Short Form Health Survey
SID	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPANC	Study of the Prevention of Anal Cancer
SSC	Saline Sodium Citrate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumor Necrosis Factor
UADE	Unanticipated (Serious) Adverse Device Effect
US	United States
VAIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
WFI	Water for Injection
WOCBP	Women of Childbearing Potential

15.0 REFERENCES

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16.0 APPENDICES