Official Title: **A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation With CELLECTRA™ 2000 Alone or in Combination With Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva**

NCT Number: NCT03180684

Document Dates:
Protocol Version 5.0: 19 December 2019
Protocol Version 3.0: 26 March 2019
Protocol Version 2.1: 01 December 2017
Protocol Version 2.0: 20 November 2017
Protocol Version 1.3: 21 April 2017
Protocol Version 1.2: 24 January 2017
Protocol Version 1.1: 20 January 2017
Protocol Version 1.0: 13 January 2017

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA® 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:

Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 1.0

13 January 2017

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

[redacted]
Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

_____ _____
<Insert Principal Investigator Printed Name> Date (DDMMMYYY)

Site Number: _____

Site Name: _____

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA® 2000 Alone or in Combination With Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 20 sites in the United States (US)	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA® 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3X) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, AIS, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related medication for treatment of VIN lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL[5]** on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18[6]** in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression[7]** of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[8]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[10].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48

[9] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[10] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

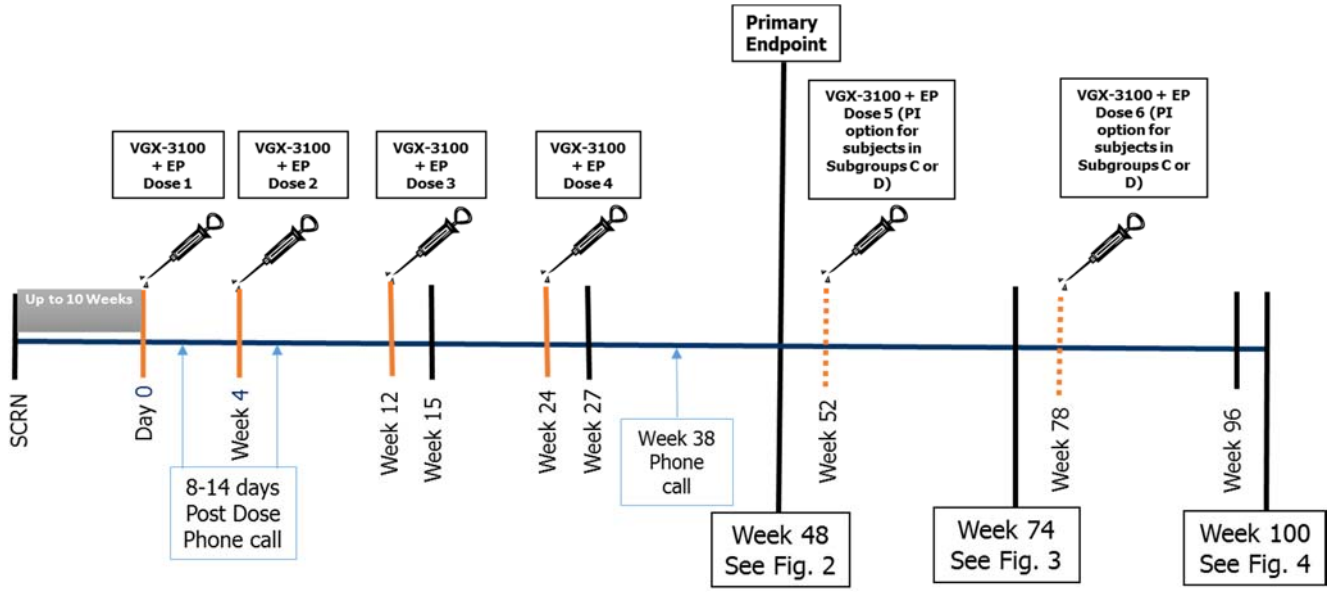
To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) and two additional PRO questions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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of potentially most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera, on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgement of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing diary provided.

Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

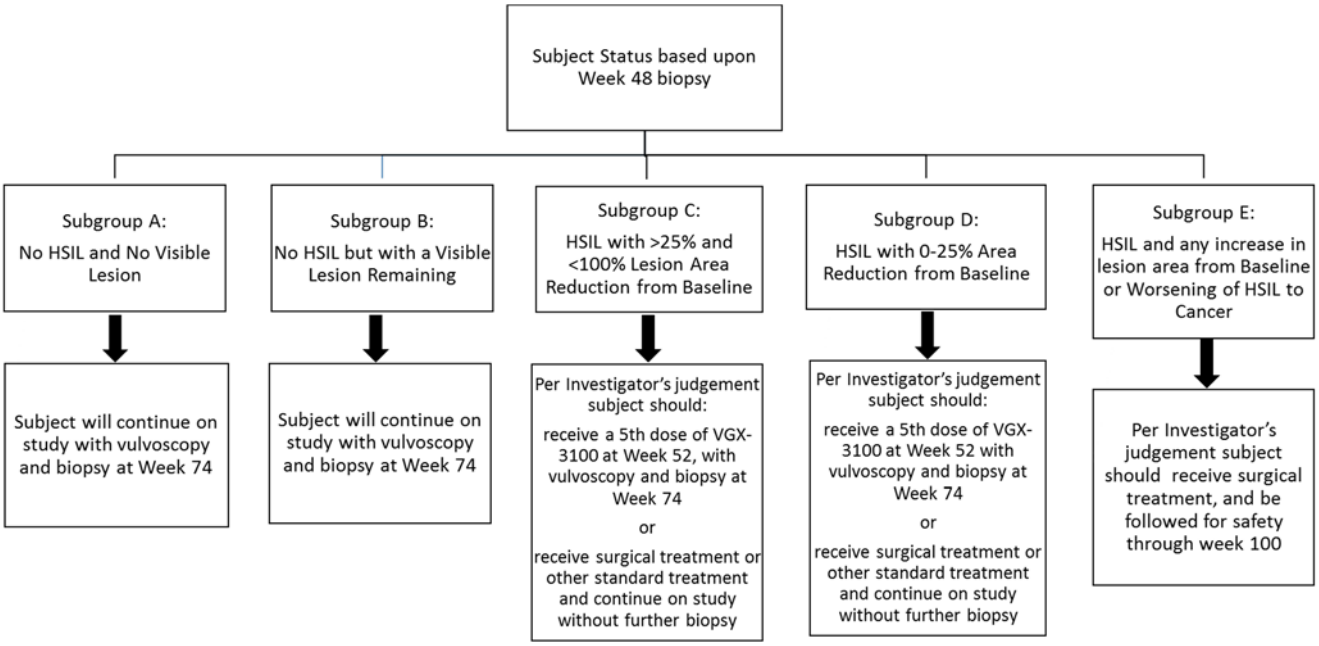
Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy. Repeat biopsies that are indicated beyond Week 48 must be taken from the same lesion, adjacent to the prior biopsy site(s) within the boundaries of the original lesion.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at

Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

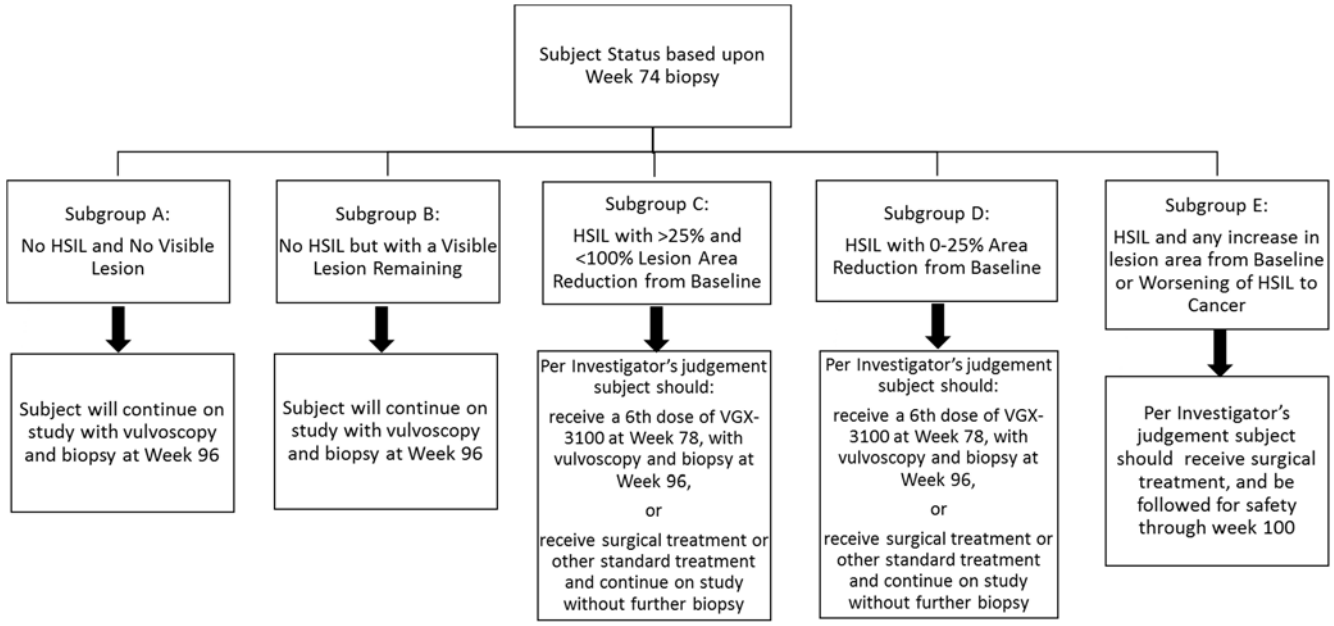
Figure 2: Decision process at Week 52



The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

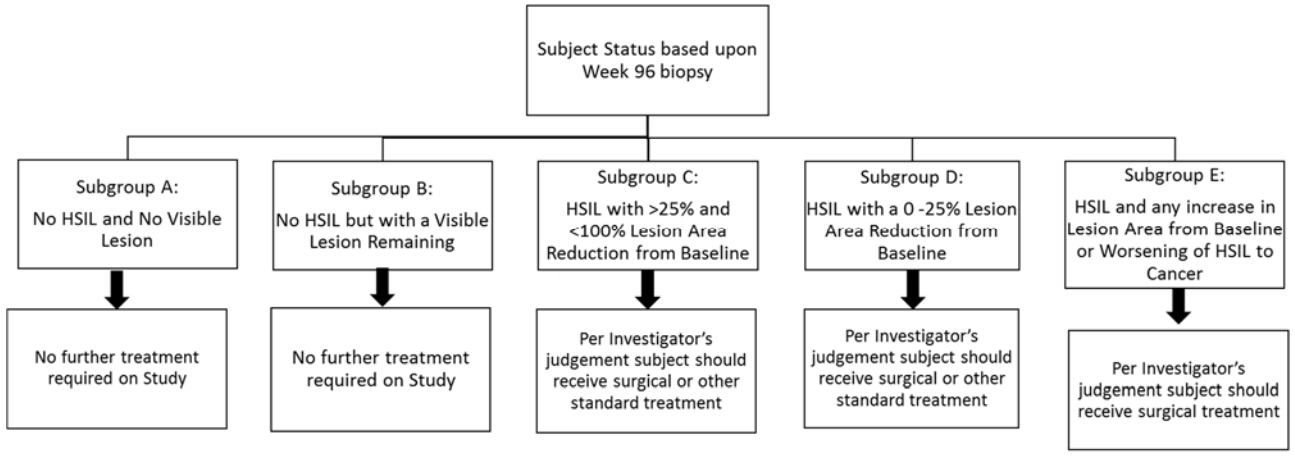
If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (ie, Subgroup E – any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medication for treatment of VIN lesions. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

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

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

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74, and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to the Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by the PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
9) Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10) History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11) Treatment for genital warts within 4 weeks prior to screening;
12) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15) Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
18) Received any non-study related non-live vaccine within 2 weeks of Day 0;
19) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21) Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22) Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial

skin cancers that only require local excision;
23) Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25) 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;
26) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27) Prior major surgery within 4 weeks of Day 0;
28) Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29) Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30) Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31) Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32) Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34) Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35) Active military service personnel;
36) Study-related staff or family members of study-related staff;
37) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X							X							
Socio-behavioral assessment	X										X					X
Inclusion criteria	X	X														
Exclusion criteria	X	X----------														-X
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]		X														
Cervical cytology, ThinPrep™ [h]	X								X		X		X		X	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Cervical colposcopy	X														X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [m]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing diary [n]		X		X		X										
Review imiquimod dosing diary				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X----------															-X
Ultrasound Measure of skin-to-muscle and related thicknesses	X															
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X		X		X	X

Abbreviations: OP; oropharynx

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 30 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Standardized high resolution digital imaging of the vulva and the associated acetowhite stained lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. Additionally, standardized high resolution digital imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen and slides from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing diary to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16 is involved in more than 85% of HPV-associated vulvar HSIL cases in the U.S.[1]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oro-pharyngeal, 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)[2].

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 5,950 new cases and 1,110 attributable deaths annually for year 2016 in the United States [3]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [4]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 70.7% [3]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [5].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [6]

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which

only high grade VIN (2/3) is classified as VIN [7]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [8]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, which encompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [9]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [10], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [11].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates exceed 30-50% with all currently available treatment regimens [12, 13].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should

extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [14].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [15]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [14]. Therefore, many patients have a fear of recurrence and progression to cancer [16].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid use of toilet paper and to rather rinse with warm water. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [17]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [18].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [17]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [18].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women [19]. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [17].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of

these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [20]. However, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [21]).

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan is used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of trial subjects for this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists (pathology adjudication committee). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related [22], is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible.

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.14). Colposcopy will also be done at baseline and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgement.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA® *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [23, 24]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by

10 to 100 fold [25, 26]. 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 [27].

This study will use the CELLECTRA® 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA® 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV 16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [28].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [15].

The current study will include an imiquimod arm with VGX-3100, to evaluate histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18, compared to the current body of knowledge in imiquimod alone.

1.1.15 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [29]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.16 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[11] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[12] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[13] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

[11] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[12] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[13] Progression is defined as advancement to carcinoma according to the Pathology Adjudication Committee by histology.

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[14]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

[14] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[15]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[16].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses.
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. A patient-reported outcome (PRO) endpoint may be obtained prior to first dose (Day 0), following each of the first doses, and at Weeks 74, and 96.

[15] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[16] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid, preferred site, or anterolateral quadriceps, alternate site) followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator.

Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgement of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing diary provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of initial biopsy.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

If HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose

of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (ie, Subgroup E - any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 3: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original biopsy site within the boundaries of the original lesion;
Acetowhite Lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original site within the boundaries of the original lesion; biopsy of lesion must include suspected area of most advanced disease
Multiple acetowhite lesions	Vulvar punch biopsies and imaging; biopsy should be conducted of the same two lesions as study entry but adjacent to the original site within the boundaries of the original lesion; biopsies must include area of most advanced and severe disease as determined at screening

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation,

or a subject who received non-study related medications for treatment of VIN lesions. Any case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology.

Table 4: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL[a] AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive non-study related medication for treatment of VIN lesions.	Subject with histologic evidence of vulvar HSIL, Adenocarcinoma-in-situ (AIS), vulvar carcinoma at evaluation AND/OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related medication for treatment of VIN lesions

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data. 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, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

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

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74 and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified

procedure (i.e. excision or biopsy) required at Week 48;

7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;

9. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10. History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11. Treatment for genital warts within 4 weeks prior to screening;
12. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16. Immunosuppression as a result of underlying illness or treatment including:
    a. History of or positive serologic test for HIV at screening;
    b. Primary immunodeficiencies;
    c. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d. Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e. History of solid organ or bone marrow transplantation;
    f. Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
18. Received any non-study related non-live vaccine within 2 weeks of Day 0;
19. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21. Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

23. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25. 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;
26. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27. Prior major surgery within 4 weeks of Day 0;
28. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35. Active military service personnel;
36. Study-related staff or family members of study-related staff;
37. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document

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 VIN, 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 she 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 she 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 1). At a minimum, the investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon®) technology. The VGX-3100 formulation to be used in this study is described in Table 5 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently

recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 5. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL] 1 mL/Vial Single Use Vial Date of Manufacture: _____ Expiry Date: _____ Refrigerate at 2-8°C CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Opthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours.

Subjects will be provided with an imiquimod dosing diary to record their use and side effects during the 20 week treatment period. The imiquimod dosing diary should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

5.7 USE OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA® 2000 Pulse Generator has a unique serial number, and each CELLECTRA® 2000 Applicator has a unique serial number. Each CELLECTRA® 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

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

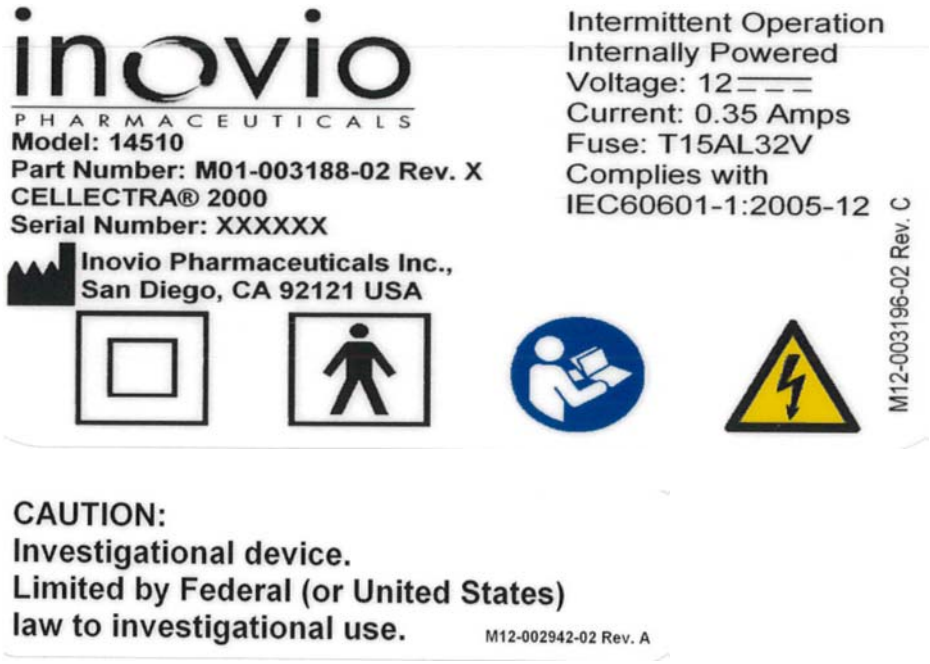
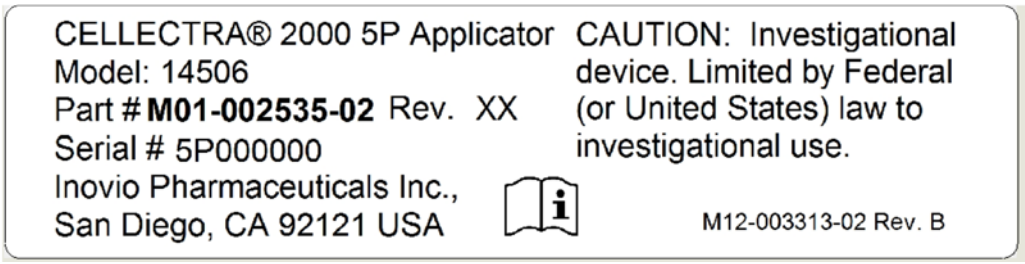
1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform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

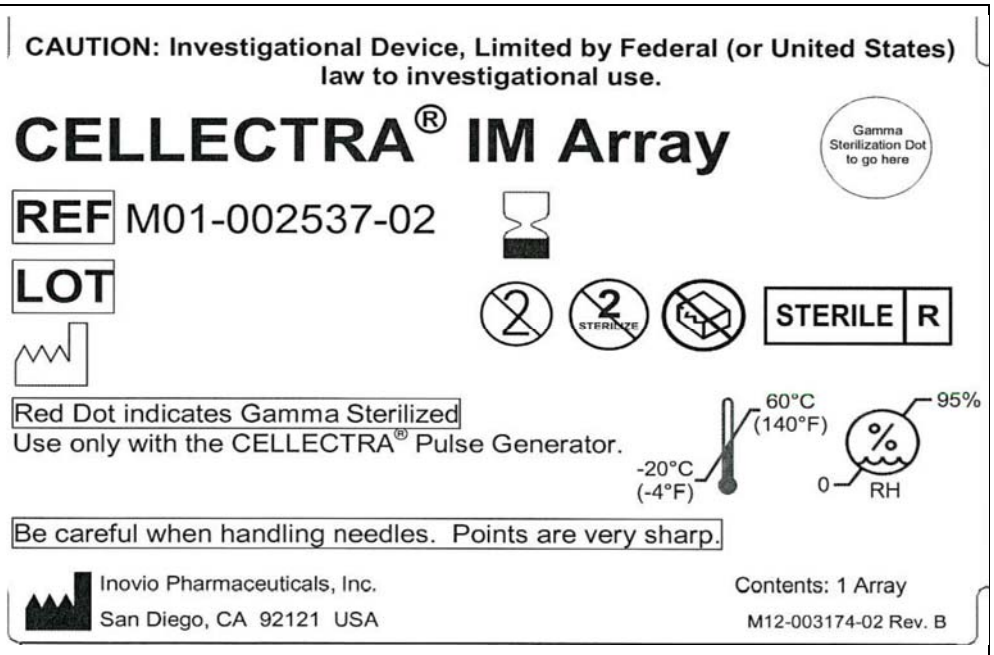
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 7 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 7. Example Labels for the CELLECTRA® 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA® 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA® 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA® IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA® 2000 serial number, applicator serial number, and array lot number. The CELLECTRA® 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

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

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes complete blood count [CBC), serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed within 30 days prior to Day 0
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Cervical cytology and ThinPrep™ for cervical HPV type
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected prior to and after biopsy at screening.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC. If residual vulvar tissue is available from entry either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.1.2 ULTRASOUND MEASURE OF SKIN-TO-MUSCLE AND RELATED THICKNESSES

Subjects who consent to participate in the ultrasound sub-study will have both right and left deltoids and one (either) quadriceps measured. The precise site of the ultrasound

within the deltoid and quadriceps will align with where EP is administered. The ultrasound measure will be performed at each of those three body sites in two manners: with no pressure applied by the technician through the probe to the tissue and separately, and with EP-like pressure applied by the technician through the probe to the tissue and separately. The "EP-like pressure" is defined as a firm push against the skin resulting in puckering of the skin by the ultrasound probe. The rationale for the differing pressures is to determine if and how much the thickness being measured will change. For each body site and pressure, three triplicate measures will be performed. The type and number of ultrasound images and replicates taken for each body site for each patient would be as follows:

Table 8. Type and Number of Ultrasound Images, by Muscle and Probe Pressure

	Right Deltoid	**Left Deltoid**	**Either Quadriceps**	**Total**
No pressure of the ultrasound probe on tissue site	3	3	3	9
EP-like pressure of the ultrasound probe on tissue site	3	3	3	9
Total number of replicate measures	6	6	6	18

Ultrasound measures will be performed during the screening period, i.e. before enrollment and hence before any administrations of VGX-3100, and will thus include both enrolled and screen-failed subjects.

Locally stored images of each ultrasound measure will be measured via digitizer or simple scale to obtain the following cross-sectional distances, for each replicate image:

- Skin to muscle distance (i.e. depth of the beginning of the muscle) = "S-M"
- Skin to bone distance (i.e. depth of the beginning of the bone) = "S-B"
- Muscle thickness (i.e. distance of the beginning to end of the muscle) = "MT", a calculated field with the following equation:

  MT = "S-B" - "S-M"

The ultrasound measures will be performed on all screened patients in this trial, thus including both enrolled patients and ultimately screen-failed patients in these sub-analyses.

Last, each patient would be asked for their handedness, i.e. whether they are they right-handed, left-handed, or ambidextrous.

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria

- Review of concomitant medications and adverse events
- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP rinse, vaginal and intra-anal swabs
- Baseline vulvoscopy
- Vulvar lesion photography

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing diary (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
  - After completing a review of PD 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.

6.2.3 WEEK 4

The following study evaluations will be performed at Week 4 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing diary and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test

- Vulvoscopy
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing diary (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12

The following study evaluations will be performed at Week 12 **prior to study treatment (± 7 days):**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing diary and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 and Week 94 unless PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression

- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing diary to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15

The following study evaluations will be performed at Week 15 (± 7 days):

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay

6.2.7 WEEK 24

The following study evaluations will be performed at Week 24 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing diary and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27

The following study evaluations will be performed at Week 27 (± 7 days):

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

6.2.9 WEEK 48

The following study evaluations will be performed at Week 48 (± 7 days):

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type

- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC
    - If residual vulvar tissue is available from entry and/or Week 48 specimen(s) either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18
- Patient Reported Outcomes

6.2.10 WEEK 52

Subjects will have a Week 52 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.11 WEEK 74

The following study evaluations will be performed at Week 74 (± 14 days):

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs

- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.12 WEEK 78

Subjects will have a Week 78 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.13 WEEK 96

The following study evaluations will be performed at Week 96 (± 14 days):

- Review of concomitant medications and adverse events

- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Cervical colposcopy
  - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.14 WEEK 100

The following study evaluations will be performed at Week 100 (± 14 days):

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.3 SAFETY EVALUATIONS

6.3.3.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

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

6.3.3.2 VITAL SIGNS

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

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate

- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.3.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.3.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.3.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.3.8 ELECTROCARDIOGRAM (ECG)

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

6.3.3.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

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

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

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

6.3.3.10 IMIQUIMOD DOSING DIARY

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the dosing diary during the 20 week treatment period. Subjects will record their symptoms, the severity of their symptoms, and the duration of symptoms and return the diary at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA® 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

Table 9 summarizes reported AEs and potential risks of VGX-3100.

Table 9. Summary of Reported Adverse Events and Potential Risks of VGX-3100 Delivered IM EP with CELLECTRA® 2000

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration
Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury[1] • Disruption of function of implanted electronic medical devices (if CELLECTRA® 2000 device is not used per User Manual)[1] • Exacerbation of unstable cardiac disease[1] • Effects on the fetus and on pregnancy

[1]device only

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Table 10 summarizes local skin reactions assessed by the Investigator in the treatment area of females taking imiquimod cream, 5% cream for external genital warts [30].

Table 10. Summary of Reported Adverse Events in 114 females taking imiquimod cream, 5% for external genital warts

	Imiquimod Cream, 5% N =114
Erythema	74 (65%)
Erosion	35 (31%)
Excoriation/Flaking	21 (18%
Edema	20 (18%)
Scabbing	4 (4%)
Induration	6 (5%)
Ulceration	9 (8%)
Vesicles	3 (3%)

*All Grades: Mild, Moderate, or Severe

Table 11 summarizes adverse reactions judged to be possibly or probably related to Imiquimod Cream, 5% and reported by more than 1% of subjects [30].

Table 11. Possibly or probably related Adverse Reactions to Imiquimod cream in > 1% of subjects

Location of reaction	**Adverse reaction**
Application Site Disorders	Burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness
Remote site reactions	Bleeding, burning, itching, pain, tenderness, tinea cruris
Body as a Whole	Fatigue, fever, influenza-like symptoms
Central and Peripheral Nervous System Disorders	Headache
Gastro-Intestinal System Disorders	Diarrhea
Musculo-Skeletal System Disorders	Myalgia

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO EP PROCEDURE

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

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

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.3.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

Table 12. Grading Scale for Injection Site Reactions

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. The following PRO questionnaires will be used:

1. **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [31]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [32, 33] and will be administered with EQ-5D-5L as described below.
3. **WOMAN-PRO (WOMen with vulvAr Neoplasia):** for measure of outcomes related to vulvar HSIL [18].

    WOMAN-PRO and EQ-5D-5L will be administered together at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)

- Week 96
- Week 100

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.

4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered at Week 48 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

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

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

A 4 mm vulvar punch biopsy sample will be obtained at Screening, Weeks 48, 74, and 96, and will be sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a 4 mm vulvar biopsy will be obtained from two regions of most advanced and severe disease as judged by the investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching vulvar biopsy samples to eliminate potential interference with the results of HPV testing.

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Screening and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep™ test kits at Screening, Weeks 27, 48, 74 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions which appears to have the highest likelihood according to the investigator of most advanced disease and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. An unscheduled biopsy may be performed at the discretion of the investigator if there is suspicion of disease progression. Guidelines for managing the findings of unscheduled biopsies for suspected disease progression are described in Table 13. Consult the Medical Monitor for any planned departures from these guidelines.

Table 13: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

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

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

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

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

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be

overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

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

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

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

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

accordingly. Causality should be assessed by the investigator as “yes, related” or “no, unrelated” by the following criteria:

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

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

7.1.10 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 related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded

from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)

- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA® 2000 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
- Grade 3 or greater laboratory abnormalities

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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Three or more subjects in the same treatment arm discontinue due to an AE related to the Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE or Grade 4 AE) or death assessed as related to Study Treatment;
- Two or more subjects within a treatment arm experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Four or more subjects across all treatment arms experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Any report of anaphylaxis assessed as related to Study Treatment.

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.6 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.7 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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: safety.inovio@apcerls.com [redacted]
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.6 and 7.1.7).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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

Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

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

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures, effect of needle depth into muscle on efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (within 10 weeks prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: p≤ 0.02 *vs*. H1: p > 0.02, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and HLA results. As these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and needle depth into muscle. A logistic regression model which models the primary endpoint versus these results and treatment group as regressor variables will be used.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, 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.

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing diary during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

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

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 three pathologists. Each specimen will be read by two pathologists independently in a masked fashion. If the two pathologists agree on the diagnosis then no further action is required and the clinical disease status for the subject will be established. If there is disagreement between the first two pathologists, the third pathologist will review and if there is agreement among any two of the three diagnoses, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached.

10.4.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
  - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
  - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor

- Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
- Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the study facilities continue to be acceptable
- Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECC	Endocervical Curettage
EDC	Electronic Data Capture
EP	Electroporation with CELLECTRA® 2000
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular

IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PCR	Polymerase Chain Reaction
PBMC	Peripheral Blood Mononuclear Cells
PD	Participant Diary
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential

13. REFERENCES

1. Bruni L B-RL, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. Human Papillomavirus and Related Diseases in United States of America. Summary Report 2016-02-26. . In. Edited by Centre). IICoHaCHI; 2016.
2. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.
3. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.
4. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.
5. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.
6. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.
7. Sideri M JR, Wilkinson EJ, Preti M, Heller DS, Scurry J, Haefner H, Neill S. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.
8. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.
9. Inovio Pharmaceuticals. Unpublished assessment. 2015.
10. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.
11. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.
12. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.
13. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.
14. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.
15. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

16. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

17. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

18. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

19. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

20. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

21. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

22. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

23. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

24. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

25. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

26. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

27. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

28. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

29. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

30. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

31. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

32. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

33. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA® 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 1.1
20 January 2017

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]

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

PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

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

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

_____ _____
<Insert Principal Investigator Printed Name> Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.0 dated 13 January 2017 to Version 1.1 dated 20 January 2017. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. An imiquimod dosing log will be implemented to collect imiquimod administration dates, instead of an imiquimod dosing diary. Subjects will be instructed to contact their study site to report symptoms. This change has been made to simplify the collection of information from subjects randomized to VGX3100 + imiquimod and is reflected in the following sections:
    - Section 6.3.3.10 – Title changed from 'Imiquimod Dosing Diary' to 'Imiquimod Dosing Log' and instructions changed to have subjects contact study personnel to report symptoms.
    - All references to imiquimod dosing diary have been changed to imiquimod dosing log throughout the protocol.
2. Timing of administration of the global PRO questions have been changed from Week 48 to Week 52 to allow the subject time to assess quality of life after the Week 48 biopsy. This change is reflected in the following sections:
    - Section 6.8 – Collection timepoint moved from Week 48 to Week 52
    - Schedule of Events – 'X' added to PRO measure at Week 52

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA® 2000 Alone or in Combination With Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 20 sites in the United States (US)	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA® 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3X) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, AIS, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related medication for treatment of VIN lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL[5]** on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18[6]** in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression[7]** of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[8]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[10].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48

[9] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[10] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

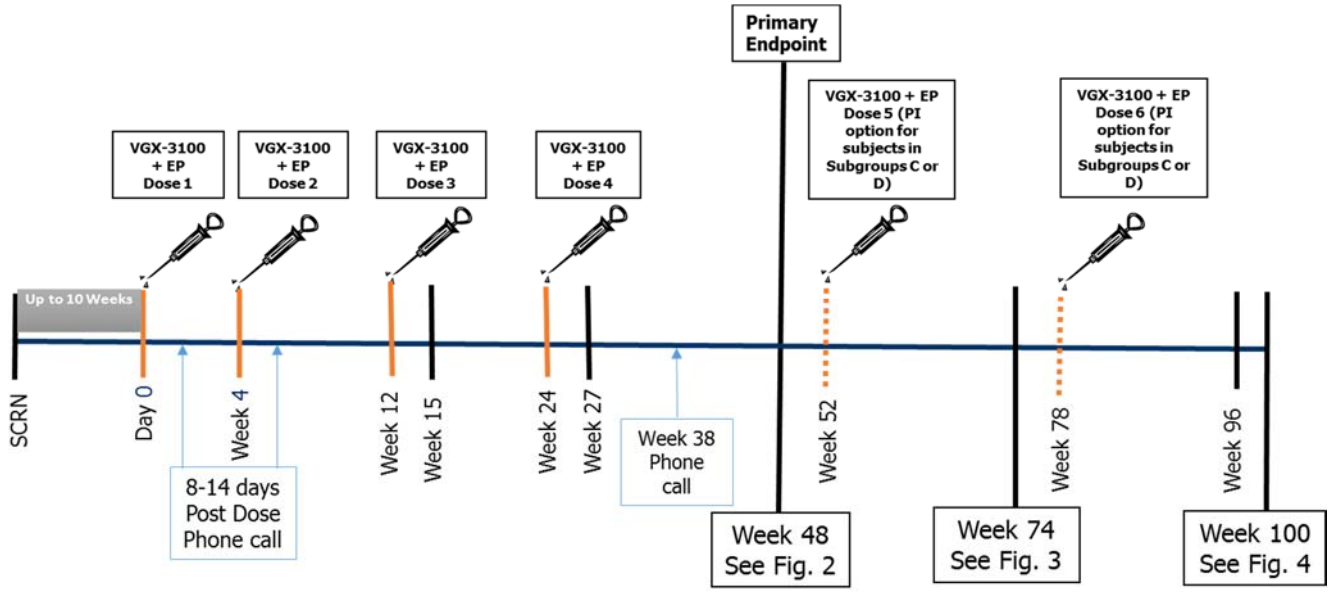
To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) and two additional PRO questions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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of potentially most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera, on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgement of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

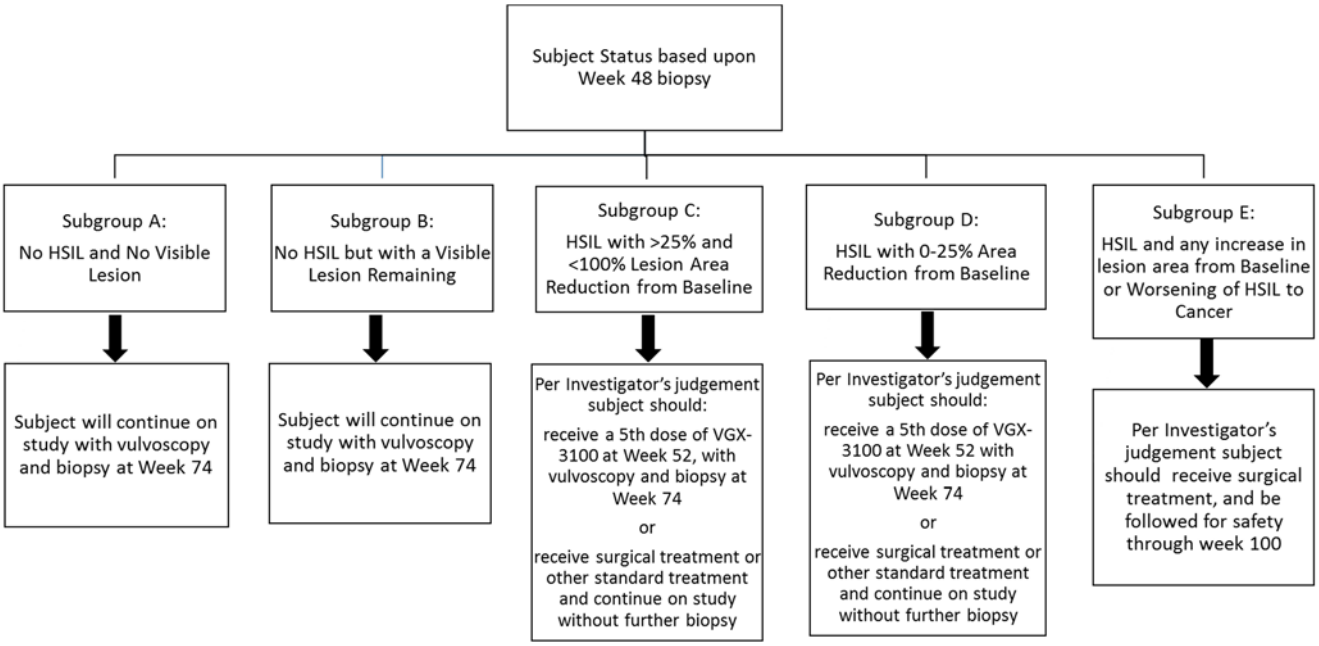
Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy. Repeat biopsies that are indicated beyond Week 48 must be taken from the same lesion, adjacent to the prior biopsy site(s) within the boundaries of the original lesion.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at

Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

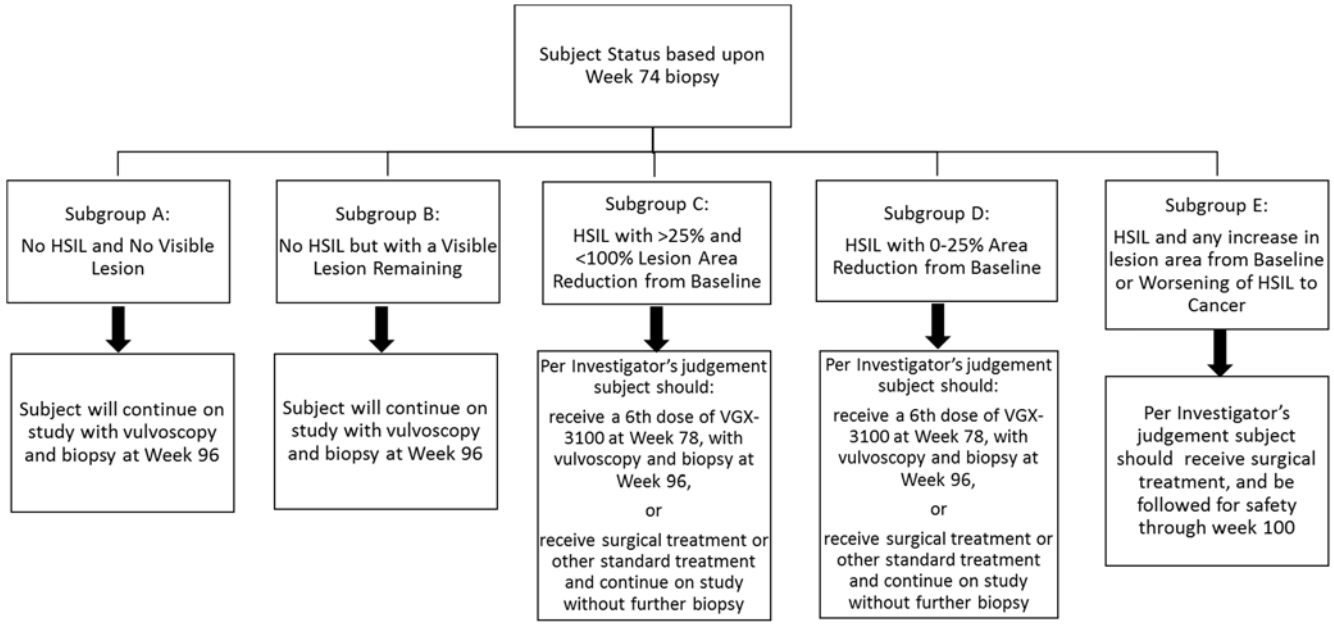
Figure 2: Decision process at Week 52



The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

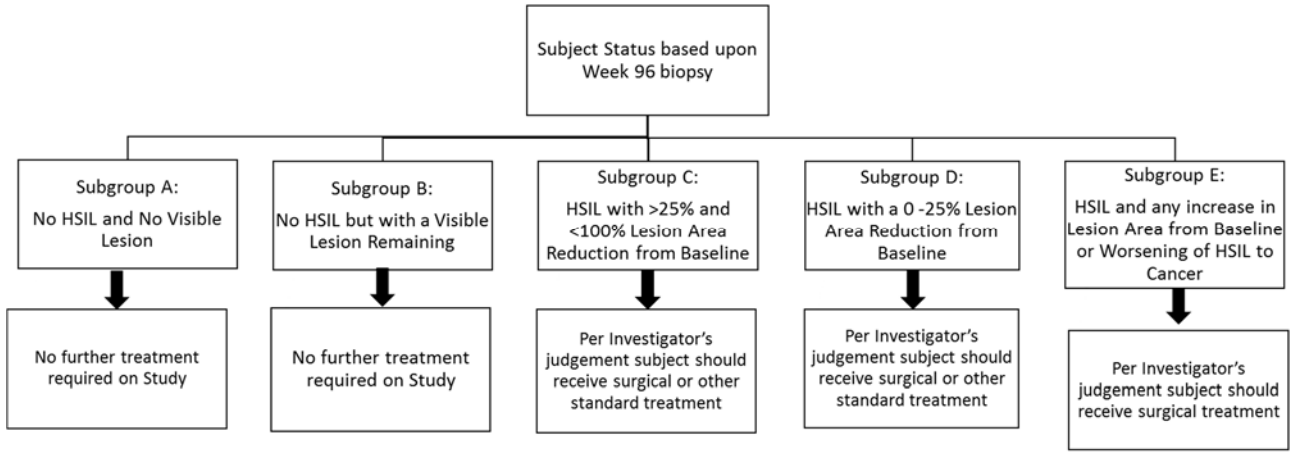
If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (ie, Subgroup E – any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medication for treatment of VIN lesions. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

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

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

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74, and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to the Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by the PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
9) Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10) History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11) Treatment for genital warts within 4 weeks prior to screening;
12) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15) Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
18) Received any non-study related non-live vaccine within 2 weeks of Day 0;
19) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21) Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22) Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial

skin cancers that only require local excision;
23) Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25) 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;
26) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27) Prior major surgery within 4 weeks of Day 0;
28) Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29) Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30) Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31) Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32) Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34) Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35) Active military service personnel;
36) Study-related staff or family members of study-related staff;
37) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X							X							
Socio-behavioral assessment	X										X					X
Inclusion criteria	X	X														
Exclusion criteria	X	X----------														X
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]		X														
Cervical cytology, ThinPrep™ [h]	X								X		X		X		X	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Cervical colposcopy	X														X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [m]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X----------															X
Ultrasound Measure of skin-to-muscle and related thicknesses	X															
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

Abbreviations: OP; oropharynx

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 30 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Standardized high resolution digital imaging of the vulva and the associated acetowhite stained lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. Additionally, standardized high resolution digital imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen and slides from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16 is involved in more than 85% of HPV-associated vulvar HSIL cases in the U.S.[1]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oro-pharyngeal, 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)[2].

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 5,950 new cases and 1,110 attributable deaths annually for year 2016 in the United States [3]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [4]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 70.7% [3]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [5].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [6]

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which

only high grade VIN (2/3) is classified as VIN [7]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [8]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, which encompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [9]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [10], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [11].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates exceed 30-50% with all currently available treatment regimens [12, 13].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should

extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [14].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [15]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [14]. Therefore, many patients have a fear of recurrence and progression to cancer [16].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid use of toilet paper and to rather rinse with warm water. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [17]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [18].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [17]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [18].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women [19]. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [17].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of

these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [20]. However, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [21]).

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan is used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of trial subjects for this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists (pathology adjudication committee). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related [22], is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible.

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.14). Colposcopy will also be done at baseline and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgement.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA® *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [23, 24]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by

10 to 100 fold [25, 26]. 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 [27].

This study will use the CELLECTRA® 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA® 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV 16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [28].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [15].

The current study will include an imiquimod arm with VGX-3100, to evaluate histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18, compared to the current body of knowledge in imiquimod alone.

1.1.15 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [29]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.16 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[11] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[12] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[13] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

[11] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[12] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[13] Progression is defined as advancement to carcinoma according to the Pathology Adjudication Committee by histology.

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[14]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

[14] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[15]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[16].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses.
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. A patient-reported outcome (PRO) endpoint may be obtained prior to first dose (Day 0), following each of the first doses, and at Weeks 74, and 96.

[15] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[16] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid, preferred site, or anterolateral quadriceps, alternate site) followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator.

Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgement of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of initial biopsy.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

If HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose

of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (ie, Subgroup E - any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 3: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original biopsy site within the boundaries of the original lesion;
Acetowhite Lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original site within the boundaries of the original lesion; biopsy of lesion must include suspected area of most advanced disease
Multiple acetowhite lesions	Vulvar punch biopsies and imaging; biopsy should be conducted of the same two lesions as study entry but adjacent to the original site within the boundaries of the original lesion; biopsies must include area of most advanced and severe disease as determined at screening

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation,

or a subject who received non-study related medications for treatment of VIN lesions. Any case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology.

Table 4: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL[a] AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive non-study related medication for treatment of VIN lesions.	Subject with histologic evidence of vulvar HSIL, Adenocarcinoma-in-situ (AIS), vulvar carcinoma at evaluation AND/OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related medication for treatment of VIN lesions

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data. 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, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

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

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74 and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified

procedure (i.e. excision or biopsy) required at Week 48;

7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;

9. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10. History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11. Treatment for genital warts within 4 weeks prior to screening;
12. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16. Immunosuppression as a result of underlying illness or treatment including:
    a. History of or positive serologic test for HIV at screening;
    b. Primary immunodeficiencies;
    c. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d. Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e. History of solid organ or bone marrow transplantation;
    f. Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
18. Received any non-study related non-live vaccine within 2 weeks of Day 0;
19. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21. Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

23. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25. 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;
26. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27. Prior major surgery within 4 weeks of Day 0;
28. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35. Active military service personnel;
36. Study-related staff or family members of study-related staff;
37. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document

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 VIN, 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 she 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 she 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 1). At a minimum, the investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon®) technology. The VGX-3100 formulation to be used in this study is described in Table 5 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently

recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 5. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL] 1 mL/Vial Single Use Vial Date of Manufacture: _____ Expiry Date: _____ Refrigerate at 2-8°C CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Opthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

5.7 USE OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA® 2000 Pulse Generator has a unique serial number, and each CELLECTRA® 2000 Applicator has a unique serial number. Each CELLECTRA® 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

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

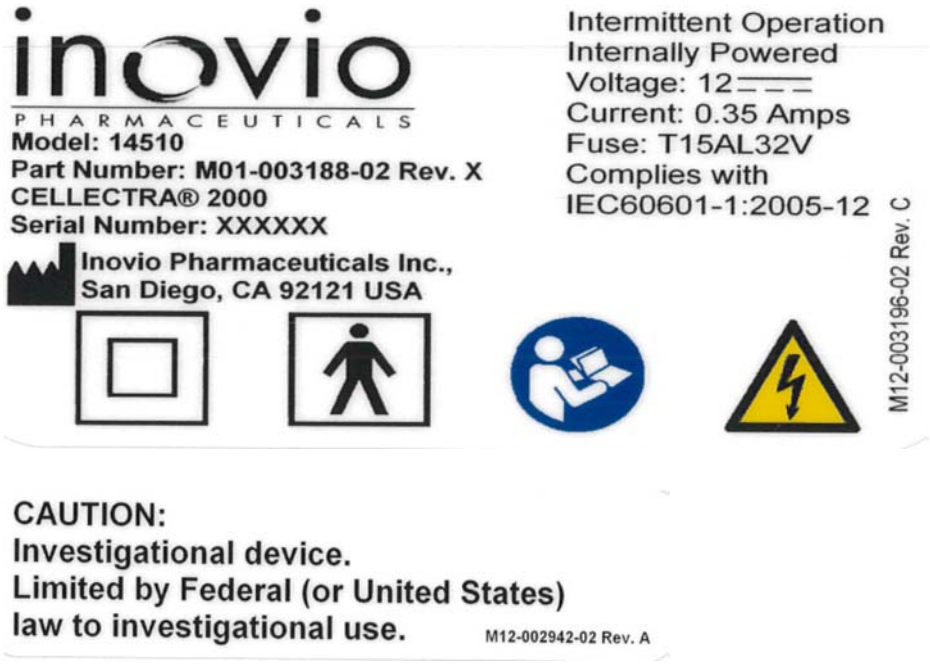
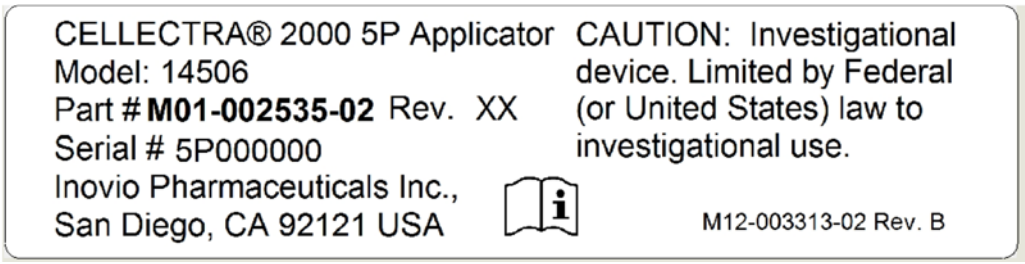
1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform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

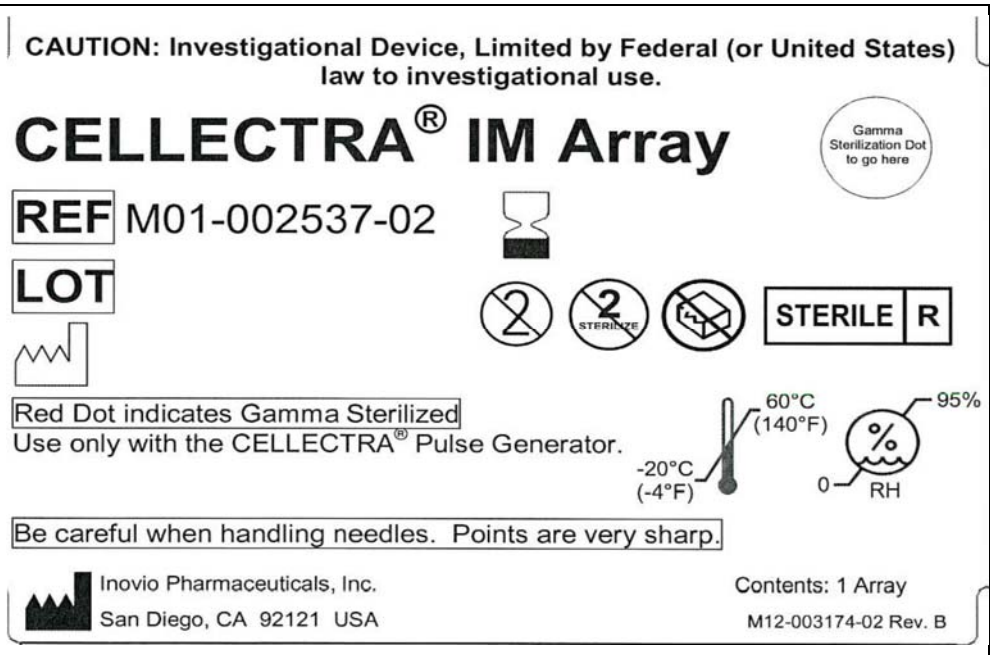
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 7 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 7. Example Labels for the CELLECTRA® 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA® 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA® 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA® IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA® 2000 serial number, applicator serial number, and array lot number. The CELLECTRA® 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

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

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes complete blood count [CBC), serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed within 30 days prior to Day 0
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Cervical cytology and ThinPrep™ for cervical HPV type
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected prior to and after biopsy at screening.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC. If residual vulvar tissue is available from entry either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.1.2 ULTRASOUND MEASURE OF SKIN-TO-MUSCLE AND RELATED THICKNESSES

Subjects who consent to participate in the ultrasound sub-study will have both right and left deltoids and one (either) quadriceps measured. The precise site of the ultrasound

within the deltoid and quadriceps will align with where EP is administered. The ultrasound measure will be performed at each of those three body sites in two manners: with no pressure applied by the technician through the probe to the tissue and separately, and with EP-like pressure applied by the technician through the probe to the tissue and separately. The "EP-like pressure" is defined as a firm push against the skin resulting in puckering of the skin by the ultrasound probe. The rationale for the differing pressures is to determine if and how much the thickness being measured will change. For each body site and pressure, three triplicate measures will be performed. The type and number of ultrasound images and replicates taken for each body site for each patient would be as follows:

Table 8. Type and Number of Ultrasound Images, by Muscle and Probe Pressure

	Right Deltoid	**Left Deltoid**	**Either Quadriceps**	**Total**
No pressure of the ultrasound probe on tissue site	3	3	3	9
EP-like pressure of the ultrasound probe on tissue site	3	3	3	9
Total number of replicate measures	6	6	6	18

Ultrasound measures will be performed during the screening period, i.e. before enrollment and hence before any administrations of VGX-3100, and will thus include both enrolled and screen-failed subjects.

Locally stored images of each ultrasound measure will be measured via digitizer or simple scale to obtain the following cross-sectional distances, for each replicate image:

- Skin to muscle distance (i.e. depth of the beginning of the muscle) = "S-M"
- Skin to bone distance (i.e. depth of the beginning of the bone) = "S-B"
- Muscle thickness (i.e. distance of the beginning to end of the muscle) = "MT", a calculated field with the following equation:

  MT = "S-B" - "S-M"

The ultrasound measures will be performed on all screened patients in this trial, thus including both enrolled patients and ultimately screen-failed patients in these sub-analyses.

Last, each patient would be asked for their handedness, i.e. whether they are they right-handed, left-handed, or ambidextrous.

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria

- Review of concomitant medications and adverse events
- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP rinse, vaginal and intra-anal swabs
- Baseline vulvoscopy
- Vulvar lesion photography

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
  - After completing a review of PD 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.

6.2.3 WEEK 4

The following study evaluations will be performed at Week 4 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test

- Vulvoscopy
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12

The following study evaluations will be performed at Week 12 **prior to study treatment (± 7 days):**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 and Week 94 unless PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression

- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15

The following study evaluations will be performed at Week 15 (± 7 days):

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay

6.2.7 WEEK 24

The following study evaluations will be performed at Week 24 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27

The following study evaluations will be performed at Week 27 (± 7 days):

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

6.2.9 WEEK 48

The following study evaluations will be performed at Week 48 (± 7 days):

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type

- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC
    - If residual vulvar tissue is available from entry and/or Week 48 specimen(s) either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18
- Patient Reported Outcomes

6.2.10 WEEK 52

Subjects will have a Week 52 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.11 WEEK 74

The following study evaluations will be performed at Week 74 (± 14 days):

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs

- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.12 WEEK 78

Subjects will have a Week 78 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.13 WEEK 96

The following study evaluations will be performed at Week 96 (± 14 days):

- Review of concomitant medications and adverse events

- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Cervical colposcopy
  - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.14 WEEK 100

The following study evaluations will be performed at Week 100 (± 14 days):

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.3 SAFETY EVALUATIONS

6.3.3.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

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

6.3.3.2 VITAL SIGNS

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

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate

- Heart rate
- Oral temperature measured with an automated thermometer

6.3.3.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.3.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.3.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.3.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.3.8 ELECTROCARDIOGRAM (ECG)

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

6.3.3.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

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

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

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

6.3.3.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA® 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

Table 9 summarizes reported AEs and potential risks of VGX-3100.

Table 9. Summary of Reported Adverse Events and Potential Risks of VGX-3100 Delivered IM EP with CELLECTRA® 2000

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration
Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury[1] • Disruption of function of implanted electronic medical devices (if CELLECTRA® 2000 device is not used per User Manual)[1] • Exacerbation of unstable cardiac disease[1] • Effects on the fetus and on pregnancy

[1]device only

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Table 10 summarizes local skin reactions assessed by the Investigator in the treatment area of females taking imiquimod cream, 5% cream for external genital warts [30].

Table 10. Summary of Reported Adverse Events in 114 females taking imiquimod cream, 5% for external genital warts

	Imiquimod Cream, 5% N =114
Erythema	74 (65%)
Erosion	35 (31%)
Excoriation/Flaking	21 (18%
Edema	20 (18%)
Scabbing	4 (4%)
Induration	6 (5%)
Ulceration	9 (8%)
Vesicles	3 (3%)

*All Grades: Mild, Moderate, or Severe

Table 11 summarizes adverse reactions judged to be possibly or probably related to Imiquimod Cream, 5% and reported by more than 1% of subjects [30].

Table 11. Possibly or probably related Adverse Reactions to Imiquimod cream in > 1% of subjects

Location of reaction	**Adverse reaction**
Application Site Disorders	Burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness
Remote site reactions	Bleeding, burning, itching, pain, tenderness, tinea cruris
Body as a Whole	Fatigue, fever, influenza-like symptoms
Central and Peripheral Nervous System Disorders	Headache
Gastro-Intestinal System Disorders	Diarrhea
Musculo-Skeletal System Disorders	Myalgia

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO EP PROCEDURE

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

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

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.3.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

Table 12. Grading Scale for Injection Site Reactions

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. The following PRO questionnaires will be used:

1. **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [31]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [32, 33] and will be administered with EQ-5D-5L as described below.
3. **WOMAN-PRO (WOMen with vulvAr Neoplasia):** for measure of outcomes related to vulvar HSIL [18].

    WOMAN-PRO and EQ-5D-5L will be administered together at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)

- Week 96 (after biopsy or surgical excision)
- Week 100

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.

4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

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

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

A 4 mm vulvar punch biopsy sample will be obtained at Screening, Weeks 48, 74, and 96, and will be sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a 4 mm vulvar biopsy will be obtained from two regions of most advanced and severe disease as judged by the investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching vulvar biopsy samples to eliminate potential interference with the results of HPV testing.

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Screening and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep™ test kits at Screening, Weeks 27, 48, 74 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions which appears to have the highest likelihood according to the investigator of most advanced disease and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. An unscheduled biopsy may be performed at the discretion of the investigator if there is suspicion of disease progression. Guidelines for managing the findings of unscheduled biopsies for suspected disease progression are described in Table 13. Consult the Medical Monitor for any planned departures from these guidelines.

Table 13: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

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

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

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

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

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be

overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

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

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

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

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

accordingly. Causality should be assessed by the investigator as “yes, related” or “no, unrelated” by the following criteria:

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

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

7.1.10 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 related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded

from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)

- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA® 2000 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
- Grade 3 or greater laboratory abnormalities

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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Three or more subjects in the same treatment arm discontinue due to an AE related to the Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE or Grade 4 AE) or death assessed as related to Study Treatment;
- Two or more subjects within a treatment arm experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Four or more subjects across all treatment arms experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Any report of anaphylaxis assessed as related to Study Treatment.

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.6 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.7 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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: safety.inovio@apcerls.com [redacted]
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.6 and 7.1.7).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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

Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

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

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures, effect of needle depth into muscle on efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (within 10 weeks prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: p≤ 0.02 *vs*. H1: p > 0.02, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and HLA results. As these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and needle depth into muscle. A logistic regression model which models the primary endpoint versus these results and treatment group as regressor variables will be used.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, 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.

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

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

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 three pathologists. Each specimen will be read by two pathologists independently in a masked fashion. If the two pathologists agree on the diagnosis then no further action is required and the clinical disease status for the subject will be established. If there is disagreement between the first two pathologists, the third pathologist will review and if there is agreement among any two of the three diagnoses, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached.

10.4.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
  - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
  - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor

- Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
- Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the study facilities continue to be acceptable
- Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECC	Endocervical Curettage
EDC	Electronic Data Capture
EP	Electroporation with CELLECTRA® 2000
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular

IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PCR	Polymerase Chain Reaction
PBMC	Peripheral Blood Mononuclear Cells
PD	Participant Diary
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential

13. REFERENCES

1. Bruni L B-RL, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. Human Papillomavirus and Related Diseases in United States of America. Summary Report 2016-02-26. . In. Edited by Centre). IICoHaCHI; 2016.
2. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.
3. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.
4. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.
5. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.
6. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.
7. Sideri M JR, Wilkinson EJ, Preti M, Heller DS, Scurry J, Haefner H, Neill S. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.
8. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.
9. Inovio Pharmaceuticals. Unpublished assessment. 2015.
10. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.
11. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.
12. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.
13. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.
14. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.
15. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

16. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

17. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

18. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

19. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

20. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

21. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

22. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

23. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

24. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

25. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

26. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

27. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

28. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

29. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

30. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

31. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

32. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

33. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA® 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 1.2
24 January 2017

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]

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

Date

PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

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

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

_____ _____
<Insert Principal Investigator Printed Name> Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.1 dated 20 January 2017 to Version 1.2 dated 24 January 2017. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. The WOMAN-PRO instrument has been removed from the list of Patient Reported Outcomes administered in Section 6.8 since the instrument is still under development.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA® 2000 Alone or in Combination With Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 20 sites in the United States (US)	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA® 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3X) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, AIS, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related medication for treatment of VIN lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL[5]** on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18[6]** in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression[7]** of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[8]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[10].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48

[9] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[10] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 52, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

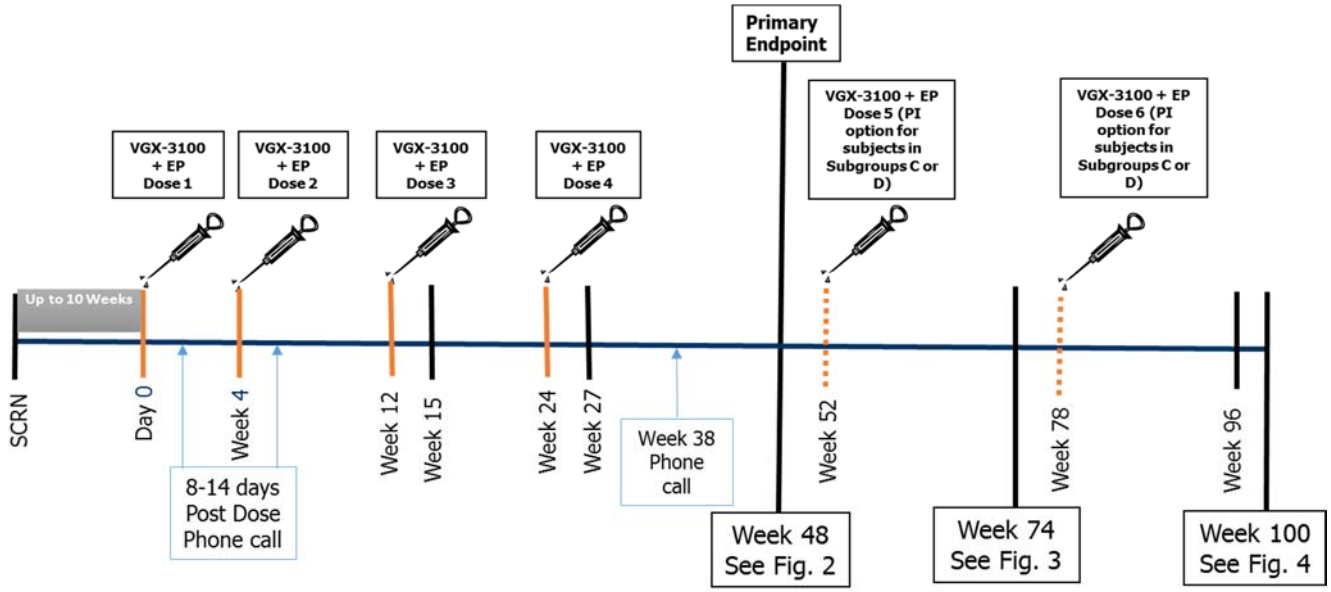
To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and two additional PRO questions assessing quality of life after surgery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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of potentially most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera, on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgement of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

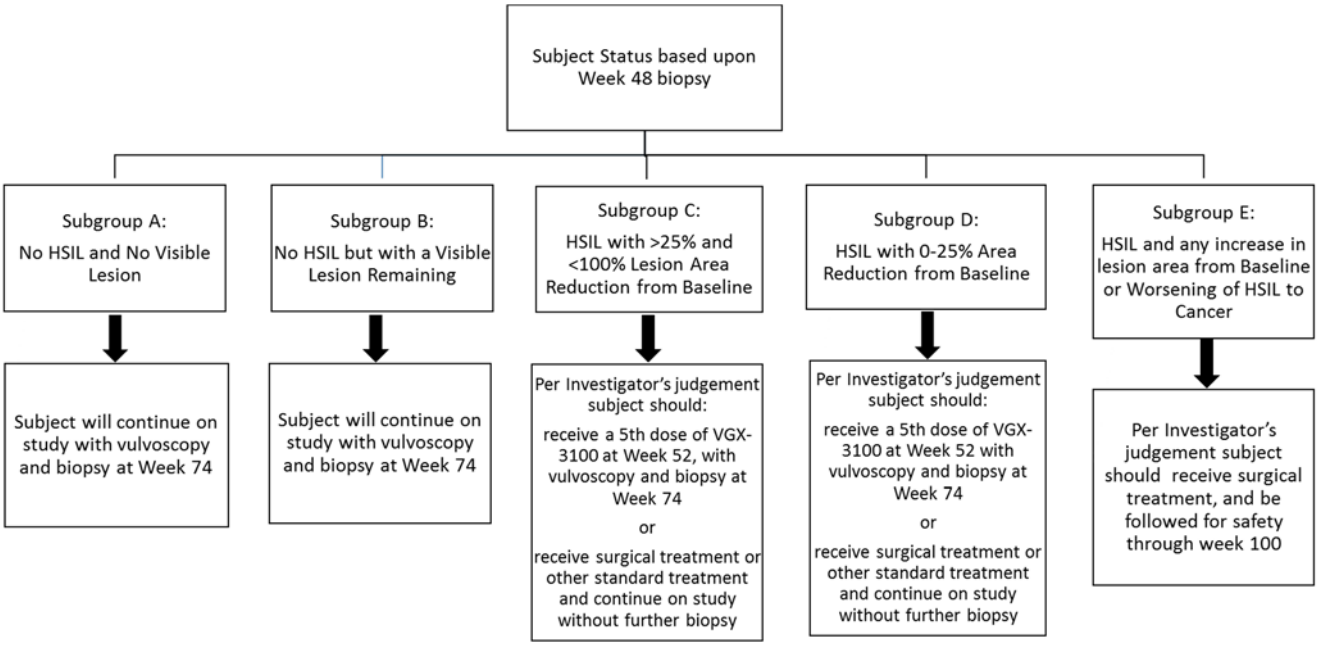
Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy. Repeat biopsies that are indicated beyond Week 48 must be taken from the same lesion, adjacent to the prior biopsy site(s) within the boundaries of the original lesion.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at

Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

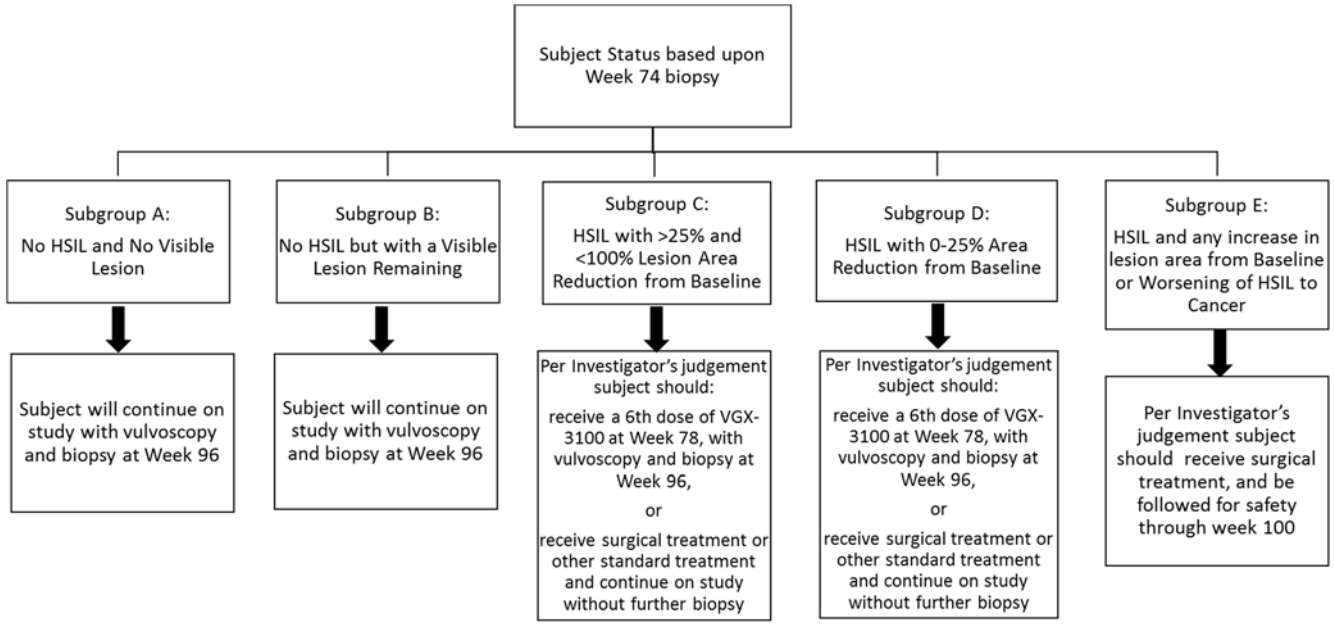
Figure 2: Decision process at Week 52



The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

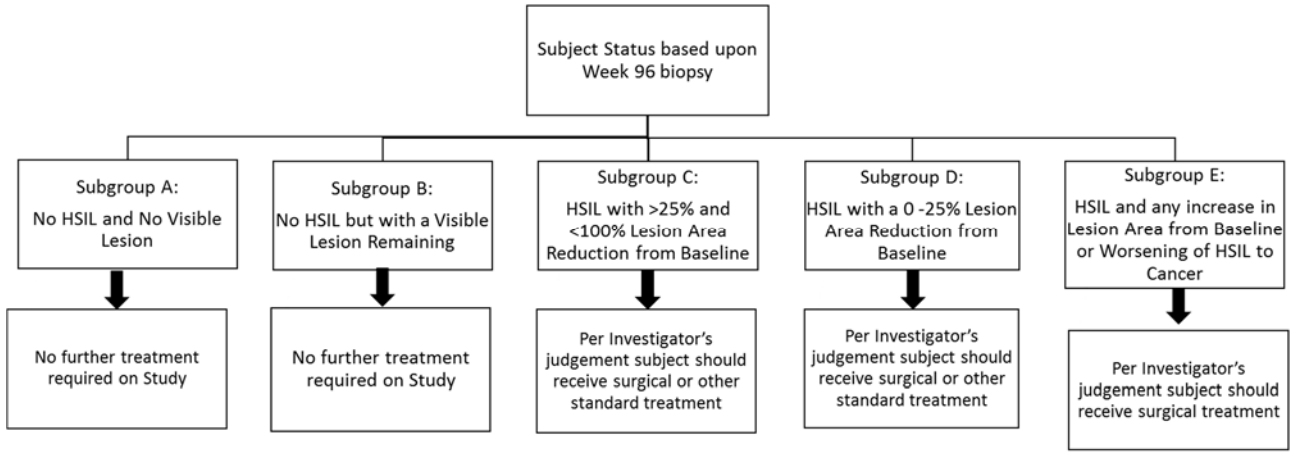
If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (ie, Subgroup E – any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medication for treatment of VIN lesions. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

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

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

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74, and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to the Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by the PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
9) Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10) History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11) Treatment for genital warts within 4 weeks prior to screening;
12) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15) Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
18) Received any non-study related non-live vaccine within 2 weeks of Day 0;
19) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21) Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22) Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial

skin cancers that only require local excision;
23) Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25) 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;
26) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27) Prior major surgery within 4 weeks of Day 0;
28) Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29) Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30) Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31) Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32) Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34) Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35) Active military service personnel;
36) Study-related staff or family members of study-related staff;
37) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X							X							
Socio-behavioral assessment	X										X					X
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]									X							
Cervical cytology, ThinPrep™ [h]	X								X		X		X		X	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Cervical colposcopy	X														X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [m]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X----------															-----X
Ultrasound Measure of skin-to-muscle and related thicknesses	X															
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

Abbreviations: OP; oropharynx

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 30 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Standardized high resolution digital imaging of the vulva and the associated acetowhite stained lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. Additionally, standardized high resolution digital imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen and slides from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36, EQ-5D-5L) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16 is involved in more than 85% of HPV-associated vulvar HSIL cases in the U.S.[1]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oro-pharyngeal, 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)[2].

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 5,950 new cases and 1,110 attributable deaths annually for year 2016 in the United States [3]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [4]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 70.7% [3]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [5].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [6]

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which

only high grade VIN (2/3) is classified as VIN [7]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [8]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, which encompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [9]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [10], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [11].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates exceed 30-50% with all currently available treatment regimens [12, 13].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should

extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [14].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [15]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [14]. Therefore, many patients have a fear of recurrence and progression to cancer [16].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid use of toilet paper and to rather rinse with warm water. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [17]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [18].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [17]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [18].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women [19]. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [17].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of

these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [20]. However, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [21]).

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan is used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of trial subjects for this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists (pathology adjudication committee). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related [22], is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible.

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.14). Colposcopy will also be done at baseline and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgement.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA® *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [23, 24]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by

10 to 100 fold [25, 26]. 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 [27].

This study will use the CELLECTRA® 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA® 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV 16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [28].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [15].

The current study will include an imiquimod arm with VGX-3100, to evaluate histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18, compared to the current body of knowledge in imiquimod alone.

1.1.15 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [29]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.16 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[11] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[12] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[13] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

[11] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[12] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[13] Progression is defined as advancement to carcinoma according to the Pathology Adjudication Committee by histology.

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[14]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

[14] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[15]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[16].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy.	7. Ultrasound-measured skin-to-muscle, skin-to-bone, and muscle thicknesses.
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 52, 74, 96 and 100.

[15] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[16] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid, preferred site, or anterolateral quadriceps, alternate site) followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in

lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgement of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of initial biopsy.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

If HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and

biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 3). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (ie, Subgroup E - any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 3: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original biopsy site within the boundaries of the original lesion;
Acetowhite Lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original site within the boundaries of the original lesion; biopsy of lesion must include suspected area of most advanced disease
Multiple acetowhite lesions	Vulvar punch biopsies and imaging; biopsy should be conducted of the same two lesions as study entry but adjacent to the original site within the boundaries of the original lesion; biopsies must include area of most advanced and severe disease as determined at screening

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 4) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL, adenocarcinoma-in-situ, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medications for treatment of VIN lesions. Any

case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology.

Table 4: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL[a] AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive non-study related medication for treatment of VIN lesions.	Subject with histologic evidence of vulvar HSIL, Adenocarcinoma-in-situ (AIS), vulvar carcinoma at evaluation AND/OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related medication for treatment of VIN lesions

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data. 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, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.

- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

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

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74 and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified

procedure (i.e. excision or biopsy) required at Week 48;

7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c. Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;

9. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10. History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11. Treatment for genital warts within 4 weeks prior to screening;
12. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16. Immunosuppression as a result of underlying illness or treatment including:
    a. History of or positive serologic test for HIV at screening;
    b. Primary immunodeficiencies;
    c. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d. Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e. History of solid organ or bone marrow transplantation;
    f. Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
18. Received any non-study related non-live vaccine within 2 weeks of Day 0;
19. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21. Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

23. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25. 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;
26. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27. Prior major surgery within 4 weeks of Day 0;
28. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35. Active military service personnel;
36. Study-related staff or family members of study-related staff;
37. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document

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 VIN, 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 she 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 she 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 1). At a minimum, the investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon®) technology. The VGX-3100 formulation to be used in this study is described in Table 5 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently

recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 5. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL] 1 mL/Vial Single Use Vial Date of Manufacture: _____ Expiry Date: _____ Refrigerate at 2-8°C CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Opthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

5.7 USE OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA® 2000 Pulse Generator has a unique serial number, and each CELLECTRA® 2000 Applicator has a unique serial number. Each CELLECTRA® 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

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

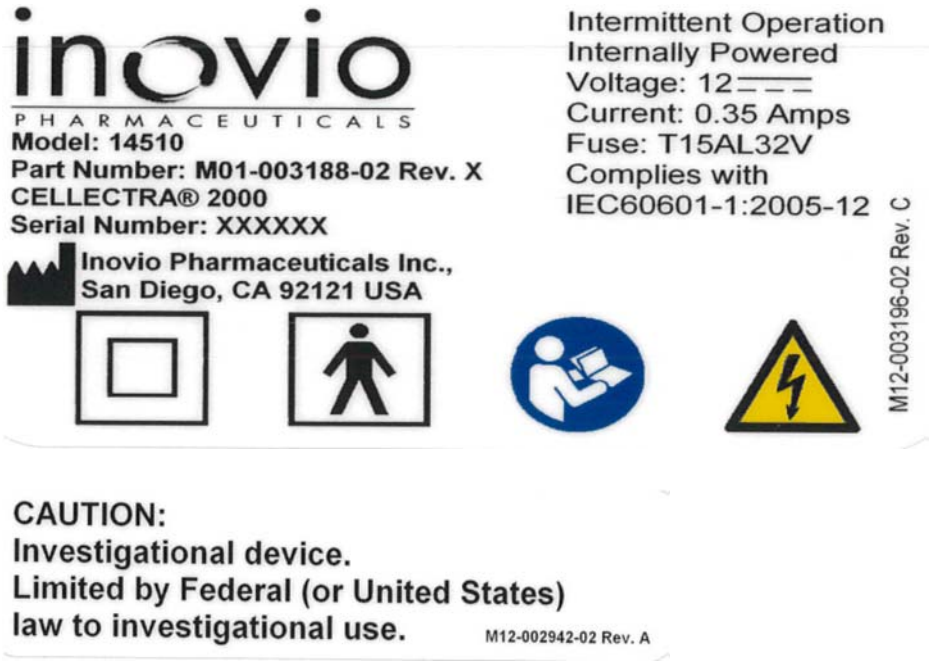
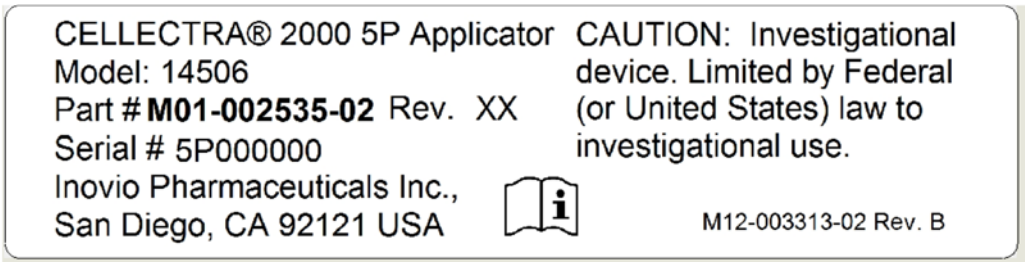
1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform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

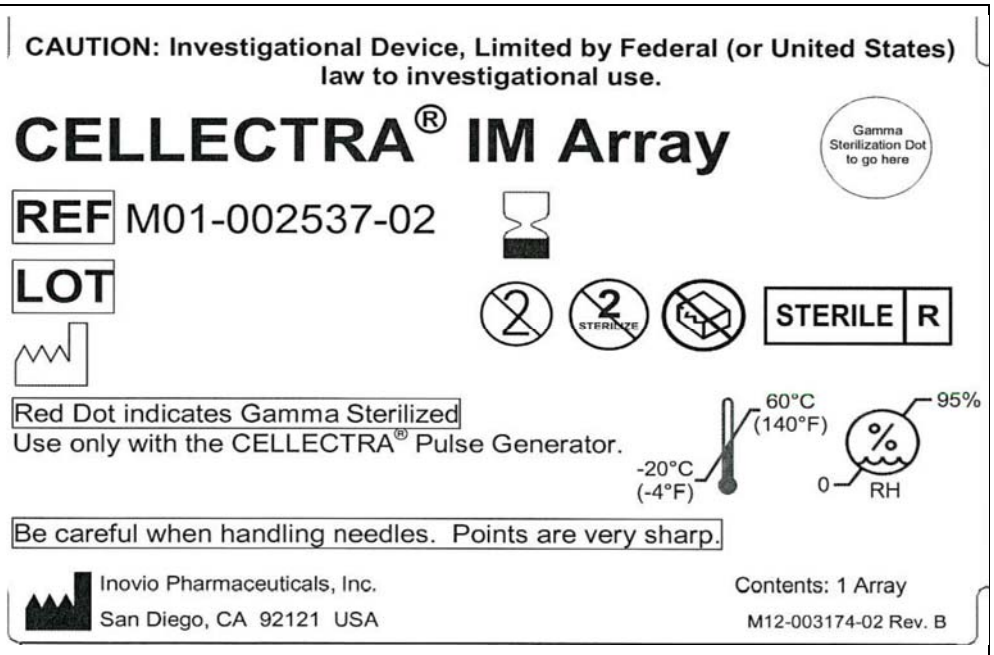
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 7 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 7. Example Labels for the CELLECTRA® 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA® 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA® 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA® IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA® 2000 serial number, applicator serial number, and array lot number. The CELLECTRA® 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. slides/samples(s) reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

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

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes complete blood count [CBC), serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed within 30 days prior to Day 0
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Cervical cytology and ThinPrep™ for cervical HPV type
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected prior to and after biopsy at screening.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC. If residual vulvar tissue is available from entry either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.1.2 ULTRASOUND MEASURE OF SKIN-TO-MUSCLE AND RELATED THICKNESSES

Subjects who consent to participate in the ultrasound sub-study will have both right and left deltoids and one (either) quadriceps measured. The precise site of the ultrasound

within the deltoid and quadriceps will align with where EP is administered. The ultrasound measure will be performed at each of those three body sites in two manners: with no pressure applied by the technician through the probe to the tissue and separately, and with EP-like pressure applied by the technician through the probe to the tissue and separately. The "EP-like pressure" is defined as a firm push against the skin resulting in puckering of the skin by the ultrasound probe. The rationale for the differing pressures is to determine if and how much the thickness being measured will change. For each body site and pressure, three triplicate measures will be performed. The type and number of ultrasound images and replicates taken for each body site for each patient would be as follows:

Table 8. Type and Number of Ultrasound Images, by Muscle and Probe Pressure

	Right Deltoid	**Left Deltoid**	**Either Quadriceps**	**Total**
No pressure of the ultrasound probe on tissue site	3	3	3	9
EP-like pressure of the ultrasound probe on tissue site	3	3	3	9
Total number of replicate measures	6	6	6	18

Ultrasound measures will be performed during the screening period, i.e. before enrollment and hence before any administrations of VGX-3100, and will thus include both enrolled and screen-failed subjects.

Locally stored images of each ultrasound measure will be measured via digitizer or simple scale to obtain the following cross-sectional distances, for each replicate image:

- Skin to muscle distance (i.e. depth of the beginning of the muscle) = "S-M"
- Skin to bone distance (i.e. depth of the beginning of the bone) = "S-B"
- Muscle thickness (i.e. distance of the beginning to end of the muscle) = "MT", a calculated field with the following equation:

  MT = "S-B" - "S-M"

The ultrasound measures will be performed on all screened patients in this trial, thus including both enrolled patients and ultimately screen-failed patients in these sub-analyses.

Last, each patient would be asked for their handedness, i.e. whether they are they right-handed, left-handed, or ambidextrous.

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria

- Review of concomitant medications and adverse events
- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP rinse, vaginal and intra-anal swabs
- Baseline vulvoscopy
- Vulvar lesion photography

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
  - After completing a review of PD 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.

6.2.3 WEEK 4

The following study evaluations will be performed at Week 4 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test

- Vulvoscopy
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12

The following study evaluations will be performed at Week 12 **prior to study treatment (± 7 days):**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 and Week 94 unless PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression

- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15

The following study evaluations will be performed at Week 15 (± 7 days):

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay

6.2.7 WEEK 24

The following study evaluations will be performed at Week 24 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27

The following study evaluations will be performed at Week 27 (± 7 days):

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48

The following study evaluations will be performed at Week 48 (± 7 days):

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test

- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC
    - If residual vulvar tissue is available from entry and/or Week 48 specimen(s) either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18
- Patient Reported Outcomes

6.2.11 WEEK 52

Subjects will have a Week 52 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.12 WEEK 74

The following study evaluations will be performed at Week 74 (± 14 days):

- Review of concomitant medications and adverse events

- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.13 WEEK 78

Subjects will have a Week 78 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.14 WEEK 96

The following study evaluations will be performed at Week 96 (± 14 days):

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.15 WEEK 100

The following study evaluations will be performed at Week 100 (± 14 days):

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment

- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.3 SAFETY EVALUATIONS

6.3.3.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

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

6.3.3.2 VITAL SIGNS

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

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

6.3.3.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.3.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.3.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.3.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.3.8 ELECTROCARDIOGRAM (ECG)

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

6.3.3.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

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

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

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

6.3.3.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA® 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

Table 9 summarizes reported AEs and potential risks of VGX-3100.

Table 9. Summary of Reported Adverse Events and Potential Risks of VGX-3100 Delivered IM EP with CELLECTRA® 2000

Very Common	• Mild to moderate injection site pain or tenderness • Malaise/fatigue, myalgia, or headache in the first few days following injection • Upper respiratory tract infection • Brief muscle contractions which may be uncomfortable • Nausea
Common	• Arthralgia • Injection site reactions such as erythema, pruritus, swelling, hematoma • Anxiety related to the administration procedure
Less Common	• Severe injection site pain or tenderness • Vasovagal reaction/lightheadedness/dizziness related to the administration procedure • Temporary bleeding at the injection site • Rash following administration
Uncommon or rare	• Injection site reactions such as laceration, induration, bruising/ecchymosis, or scab • Infection at the injection site • Muscle damage resulting in transient changes in creatine phosphokinase • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Autoimmune disease • Electrical injury[1] • Disruption of function of implanted electronic medical devices (if CELLECTRA® 2000 device is not used per User Manual)[1] • Exacerbation of unstable cardiac disease[1] • Effects on the fetus and on pregnancy

[1]device only

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Table 10 summarizes local skin reactions assessed by the Investigator in the treatment area of females taking imiquimod cream, 5% cream for external genital warts [30].

Table 10. Summary of Reported Adverse Events in 114 females taking imiquimod cream, 5% for external genital warts

	Imiquimod Cream, 5% N =114
Erythema	74 (65%)
Erosion	35 (31%)
Excoriation/Flaking	21 (18%
Edema	20 (18%)
Scabbing	4 (4%)
Induration	6 (5%)
Ulceration	9 (8%)
Vesicles	3 (3%)

*All Grades: Mild, Moderate, or Severe

Table 11 summarizes adverse reactions judged to be possibly or probably related to Imiquimod Cream, 5% and reported by more than 1% of subjects [30].

Table 11. Possibly or probably related Adverse Reactions to Imiquimod cream in > 1% of subjects

Location of reaction	Adverse reaction
Application Site Disorders	Burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness
Remote site reactions	Bleeding, burning, itching, pain, tenderness, tinea cruris
Body as a Whole	Fatigue, fever, influenza-like symptoms
Central and Peripheral Nervous System Disorders	Headache
Gastro-Intestinal System Disorders	Diarrhea
Musculo-Skeletal System Disorders	Myalgia

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO EP PROCEDURE

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

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

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.3.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

Table 12. Grading Scale for Injection Site Reactions

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. The following PRO questionnaires will be used:

1. **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [31]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [32, 33] and will be administered as described below:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)
    - Week 96 (after biopsy or surgical excision)
    - Week 100

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.

3. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

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

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

A 4 mm vulvar punch biopsy sample will be obtained at Screening, Weeks 48, 74, and 96, and will be sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a 4 mm vulvar biopsy will be obtained from two regions of most advanced and severe disease as judged by the investigator. The subject will be requested

to abstain from sexual activity and refrain from use of douching vulvar biopsy samples to eliminate potential interference with the results of HPV testing.

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Screening and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep™ test kits at Screening, Weeks 27, 48, 74 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions which appears to have the highest likelihood according to the investigator of most advanced disease and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. An unscheduled biopsy may be performed at the discretion of the investigator if there is suspicion of disease progression. Guidelines for managing the findings of unscheduled biopsies for suspected disease progression are described in Table 13. Consult the Medical Monitor for any planned departures from these guidelines.

Table 13: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the investigator may suspect disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

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

AEs do not include the following:

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

7.1.2 SERIOUS ADVERSE EVENTS

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

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

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

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

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of adenocarcinoma-in-situ or adenocarcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

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

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

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

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

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

7.1.10 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 related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

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

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA® 2000 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
- Grade 3 or greater laboratory abnormalities

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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Three or more subjects in the same treatment arm discontinue due to an AE related to the Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE or Grade 4 AE) or death assessed as related to Study Treatment;
- Two or more subjects within a treatment arm experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Four or more subjects across all treatment arms experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Any report of anaphylaxis assessed as related to Study Treatment.

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.6 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.7 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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: safety.inovio@apcerls.com [redacted]
SAFETY FAX: [redacted]
SAFETY PHONE: [redacted]

The preferred method for providing SAE forms or SAE supporting documents to the Sponsor or designee is as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.6 and 7.1.7).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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

Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or

the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures, effect of needle depth into muscle on efficacy, and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest.

Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be primary for the analysis of efficacy in this study.

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (within 10 weeks prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the method of Clopper-Pearson. Superiority will be concluded if the

one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and HLA results. As these results are categorical, relationships will be examined with contingency tables and logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and needle depth into muscle. A logistic regression model which models the primary endpoint versus these results and treatment group as regressor variables will be used.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will

be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, 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.

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

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

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review unblinded safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a

safety issue and with advising the Sponsor if it appears that regression in the VGX-3100 group is unacceptably low compared to the placebo group. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 three pathologists. Each specimen will be read by two pathologists independently in a masked fashion. If the two pathologists agree on the diagnosis then no further action is required and the clinical disease status for the subject will be established. If there is disagreement between the first two pathologists, the third pathologist will review and if there is agreement among any two of the three diagnoses, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached.

10.4.3 CLINICAL MONITORING

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

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

- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECC	Endocervical Curettage
EDC	Electronic Data Capture
EP	Electroporation with CELLECTRA® 2000
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular

IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PCR	Polymerase Chain Reaction
PBMC	Peripheral Blood Mononuclear Cells
PD	Participant Diary
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential

13. REFERENCES

1. Bruni L B-RL, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. Human Papillomavirus and Related Diseases in United States of America. Summary Report 2016-02-26. . In. Edited by Centre). IICoHaCHI; 2016.
2. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.
3. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.
4. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.
5. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.
6. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.
7. Sideri M JR, Wilkinson EJ, Preti M, Heller DS, Scurry J, Haefner H, Neill S. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.
8. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.
9. Inovio Pharmaceuticals. Unpublished assessment. 2015.
10. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.
11. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.
12. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.
13. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.
14. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.
15. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

16. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

17. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

18. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

19. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

20. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

21. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

22. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

23. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

24. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

25. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

26. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

27. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

28. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

29. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

30. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

31. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

32. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

33. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA® 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

U.S. BB-IND #13683

Version 1.3
21 April 2017

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

[redacted]
Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

_____ _____
<Insert Principal Investigator Printed Name> Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.2 dated 24 January 2017 to Version 1.3 dated 21 April 2017. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. The Ultra-sound sub-study (Section 6.1.2) has been removed from the study and will be conducted under a separate cover. Exploratory Objective # 7, Assess skin-to-muscle, skin-to-bone, and muscle thicknesses via ultrasound measure of deltoid (or quadriceps if applicable) and the correlation of needle depth into muscle with efficacy, and the corresponding time point in Table 1, Schedule of Events has consequently been removed.
2. A microRNA endpoint has been added to the exploratory objectives, to assess biomarkers that may be predictive of response. This endpoint will be assessed at Day 0, Week 15 and Week 48. Sections 6.2, 6.9 and 8.9 have been updated to reflect this addition.
3. References to adenocarcinoma or adenocarcinoma-in-situ have been removed since they are not an applicable risk for vulvar HSIL.
4. Section 5.2.1 was updated to provide details about the VGX-3100 product label.
5. CELLECTRA® 2000 specifications were added to Section 5.7 of the protocol.
6. The risk of treatment procedures to VGX-3100 and Imiquimod have been removed from Section 6.4.1 and reference made to the VGX-3100 + Imiquimod Investigator's Brochure and the Imiquimod product label, where they can be found.
7. Section 7.3.2 Stopping Rules have been updated to be consistent with the stopping rules outlined in Section 3.3.1.
8. The Sponsor Contact Information and SAE Reporting Information have been separated in Section 7.4.2.
9. DSMB review in Section 10.4.1 has been updated to remove language around unblinded data and placebo groups, which were carried over from a previous protocol and are not applicable to this study. Section 3.3.1 was updated to include histopathologic regression results to the DSMB review, to be consistent with Section 10.4.1.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA® 2000 Alone or in Combination With Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 20 sites in the United States (US)	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA® 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3X) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, AIS, or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related medication for treatment of VIN lesions.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[6] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[7] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[8]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[10].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48

[9] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[10] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 52, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

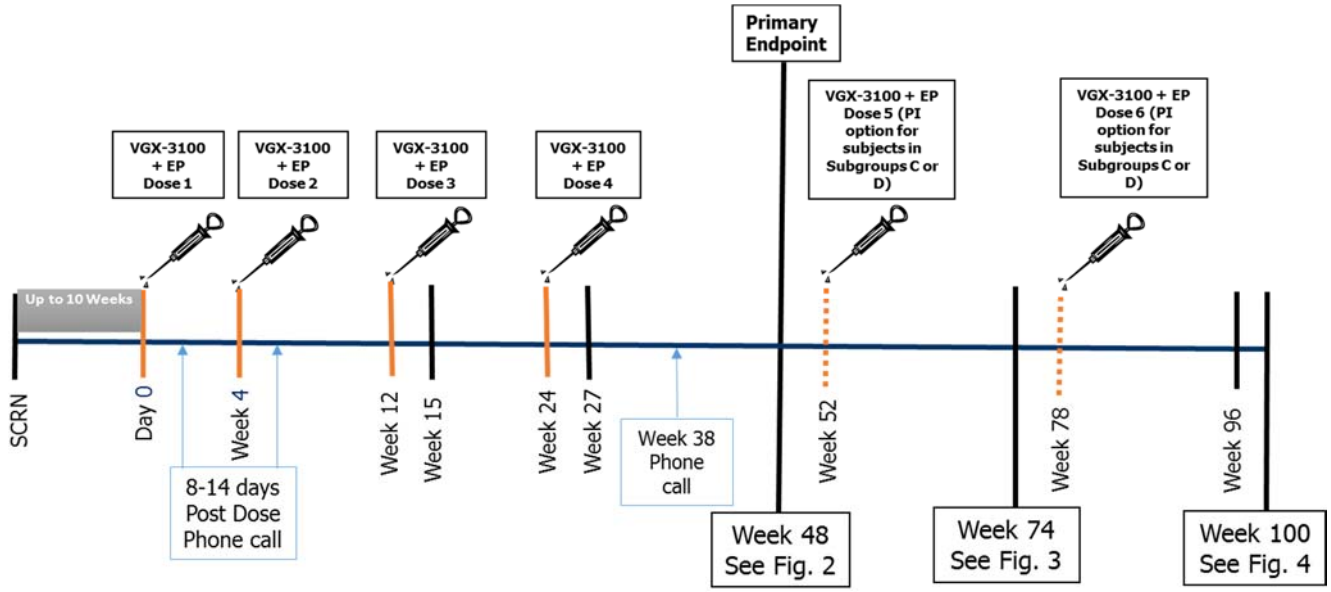
To assess quality of life and related impacts on subjects, patient-reported outcome (PRO) instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), and two additional PRO questions assessing quality of life after surgery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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of potentially most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera, on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgement of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

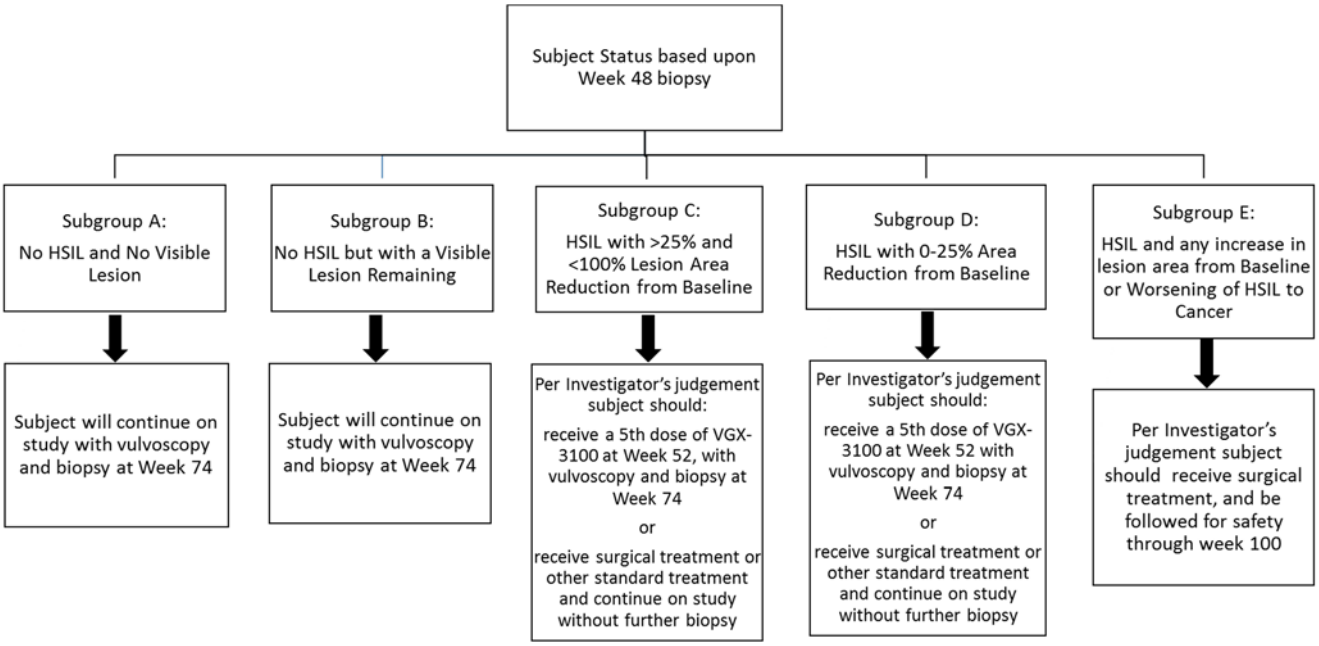
Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy. Repeat biopsies that are indicated beyond Week 48 must be taken from the same lesion, adjacent to the prior biopsy site(s) within the boundaries of the original lesion.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at

Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

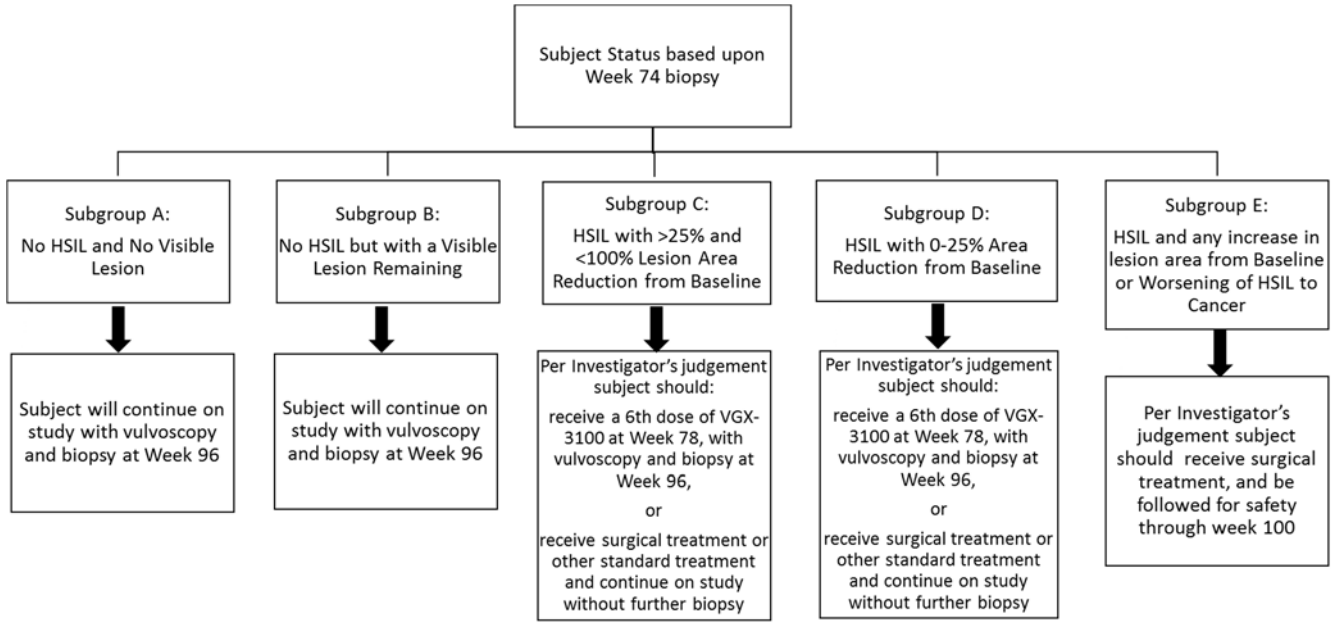
Figure 2: Decision process at Week 52



The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

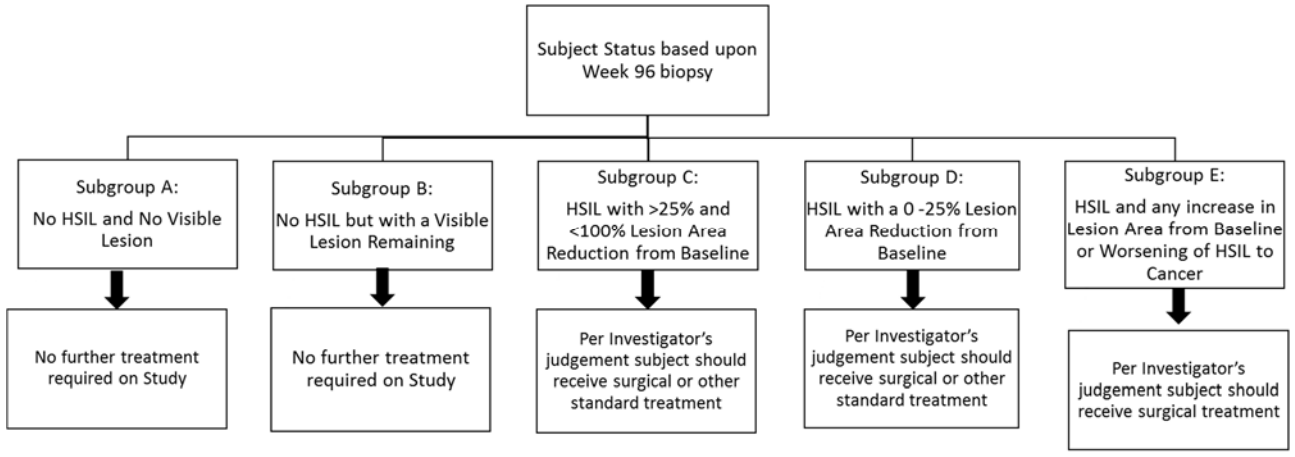
If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (ie, Subgroup E – any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medication for treatment of VIN lesions. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

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

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

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74, and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to the Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by the PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;
8. Must have vulvar HSIL that can be completely demarcated for area measurement;
9. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 12 months prior to screening;
    c) Women of Child Bearing Potential (WOCBP) are willing to use a contraceptive method with failure rate of less than 1% per year when used consistently and correctly from screening until 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
10. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
9) Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;
10) History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11) Treatment for genital warts within 4 weeks prior to screening;
12) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15) Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
18) Received any non-study related non-live vaccine within 2 weeks of Day 0;
19) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21) Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22) Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial

skin cancers that only require local excision;
23) Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
24) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25) 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;
26) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27) Prior major surgery within 4 weeks of Day 0;
28) Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29) Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30) Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31) Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32) Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34) Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35) Active military service personnel;
36) Study-related staff or family members of study-related staff;
37) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X							X							
Socio-behavioral assessment	X										X					X
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]									X							
Cervical cytology, ThinPrep™ [h]	X								X		X		X		X	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Cervical colposcopy	X														X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [m]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X----------															-X
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

Abbreviations: OP; oropharynx

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 30 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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. One additional 8.5 mL yellow (ACD) tube to be collected at Day 0, Week 15 and 48 for microRNA analysis.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Standardized high resolution digital imaging of the vulva and the associated acetowhite stained lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. Additionally, standardized high resolution digital imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) should be sent to the central pathology laboratory for immunohistochemistry (IHC) and HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36, EQ-5D-5L) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16 is involved in more than 85% of HPV-associated vulvar HSIL cases in the U.S.[1]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oro-pharyngeal, 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)[2].

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 5,950 new cases and 1,110 attributable deaths annually for year 2016 in the United States [3]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [4]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 70.7% [3]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [5].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [6]

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which

only high grade VIN (2/3) is classified as VIN [7]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [8]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, which encompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [9]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [10], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [11].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates exceed 30-50% with all currently available treatment regimens [12, 13].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should

extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [14].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [15]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [14]. Therefore, many patients have a fear of recurrence and progression to cancer [16].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid use of toilet paper and to rather rinse with warm water. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [17]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [18].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [17]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [18].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women [19]. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [17].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of

these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [20]. However, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [21]).

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan is used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of trial subjects for this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists (pathology adjudication committee). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related [22], is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible.

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.14). Colposcopy will also be done at baseline and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgement.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA® *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [23, 24]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by

10 to 100 fold [25, 26]. 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 [27].

This study will use the CELLECTRA® 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA® 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV 16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [28].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Therefore, imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [15].

The current study will include an arm to explore whether the efficacy of VGX-3100 is able to be enhanced by concomitant treatment with Imiquimod.

1.1.15 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [29]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.16 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA® 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[11] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[12] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[13] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

[11] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[12] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[13] Progression is defined as advancement to carcinoma according to the Pathology Adjudication Committee by histology.

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 48, 74 and 96 compared to baseline[14]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

[14] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized photographic imaging at Week 74 and/or Week 96 compared to baseline[15]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of $CD8^+$ and FoxP3 infiltrating cells[16].
5. Describe **virologic** clearance of HPV-16/18 from other anatomic locations outside the vulva	5. Proportion of subjects who have cleared HPV-16/18 on specimens from other anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
8. Describe patient reported outcomes for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. Patient-reported outcome (PRO) endpoints will be obtained prior to first dose (Day 0), on the day of and following each of the first four doses, and at Weeks 48, 52, 74, 96 and 100.

[15] Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[16] Additional assessments may include visualization of PD-L1, Granulysin, Perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA® 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

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

To be eligible for the study, subjects must consent to participate and have a minimum of a 4 mm vulvar punch biopsy/biopsies with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two regions of most advanced and severe disease, as judged by the investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides or tissue 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 vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid, preferred site, or anterolateral quadriceps, alternate site) followed immediately by EP with the CELLECTRA® 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in

lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgement of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced and severe disease as judged by the Investigator, and must be a minimum of 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy adjacent to the site of initial biopsy.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy adjacent to the site of the initial biopsy.

If HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and

biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but adjacent to the original site within the boundaries of the original lesion (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (ie, Subgroup E - any increase in lesion area from baseline or worsening of HSIL to cancer), the subject will receive surgical treatment per the Investigator's judgement and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 2: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original biopsy site within the boundaries of the original lesion;
Acetowhite Lesion	Vulvar punch biopsy and imaging; biopsy should be conducted of the same lesion as study entry, but adjacent to the original site within the boundaries of the original lesion; biopsy of lesion must include suspected area of most advanced disease
Multiple acetowhite lesions	Vulvar punch biopsies and imaging; biopsy should be conducted of the same two lesions as study entry but adjacent to the original site within the boundaries of the original lesion; biopsies must include area of most advanced and severe disease as determined at screening

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive non-study related medication for treatment of VIN lesions. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, and/or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related medications for treatment of VIN lesions. Any case of

histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology.

Table 3: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL[a] AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive non-study related medication for treatment of VIN lesions.	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation AND/OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related medication for treatment of VIN lesions

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data and regression/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, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.
- If three or more subjects in this study experience the same Grade 3 or 4 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, and the DSMB.
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until

a thorough investigation has been conducted by the Medical Monitor, Principal Investigator for the trial, IRB (if applicable) and the DSMB.

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

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (both Screening as well as Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and at Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize HPV infection at Screening, Week 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection in samples from study subjects taken at Screening (cervical sample only), Day 0 prior to dosing (OP, vaginal and intra-anal only) and at Weeks 27, 48, 74 and 96.

If there is residual tissue in the paraffin block after histologic diagnoses have been rendered, then unstained slides and/or the relevant paraffin blocks will be collected for immunohistochemistry (IHC) and in situ hybridization (ISH) for the presence of HPV-16/18. Whenever possible, these studies will be performed on tissue sections from the diagnostic biopsy (pre-dose) and from tissue obtained post-dose (Week 48, 74 and 96).

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Confirmed vulvar infection with HPV types 16 and/or 18 at screening;
4. Vulvar tissue specimen/slides provided to Study Pathology Adjudication Committee for diagnosis must be collected within 10 weeks prior to anticipated date of first dose of study drug;
5. Histologic evidence of vulvar HSIL as confirmed by PAC at screening;
6. Must be judged by investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
7. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of

adequate size to ensure that a visible lesion remains after 4 mm screening biopsy;

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

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. More than 10 weeks have elapsed between date of initial tissue biopsy for screening and day of first dose (i.e. Day 0);
7. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
8. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
9. Cervical lesion(s) that cannot be fully visualized on colposcopy due to extension high into cervical canal at screening;

10. History of endocervical curettage (ECC) which showed cervical HSIL indeterminate, or insufficient for diagnosis (ECC is not performed as part of study screening) and did not receive definitive treatment;
11. Treatment for genital warts within 4 weeks prior to screening;
12. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
13. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
14. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
15. Presence of any abnormal clinical laboratory values greater than Grade 1 per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 within 30 days prior to Day 0 **or** less than Grade 1 but deemed clinically significant by the investigator;
16. Immunosuppression as a result of underlying illness or treatment including:
    a. History of or positive serologic test for HIV at screening;
    b. Primary immunodeficiencies;
    c. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d. Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e. History of solid organ or bone marrow transplantation;
    f. Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
17. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
18. Received any non-study related non-live vaccine within 2 weeks of Day 0;
19. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of Day 0;
20. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the investigator;
21. Current or history of clinically significant, medically unstable disease which, in the judgement 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);
22. Malignancy or treatment for malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
23. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of

Day 0;

24. History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
25. 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;
26. Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
27. Prior major surgery within 4 weeks of Day 0;
28. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
29. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
30. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
31. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
32. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
33. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
34. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
35. Active military service personnel;
36. Study-related staff or family members of study-related staff;
37. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document

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 VIN, 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 she 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 she 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 1). At a minimum, the investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon®) technology. The VGX-3100 formulation to be used in this study is described in Table 4 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently

recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 4. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. The actual product label names the product as VGX-3100X; the “X” designation was included to differentiate the current buffer formulation from a previous formulation of VGX-3100 in water. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL] 1 mL/Vial Single Use Vial Date of Manufacture: _____ Expiry Date: _____ Refrigerate at 2-8°C CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Opthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

5.7 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA® 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA® 2000 device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA® 2000 Pulse Generator has a unique serial number, and each CELLECTRA® 2000 Applicator has a unique serial number. Each CELLECTRA® 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

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

1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.

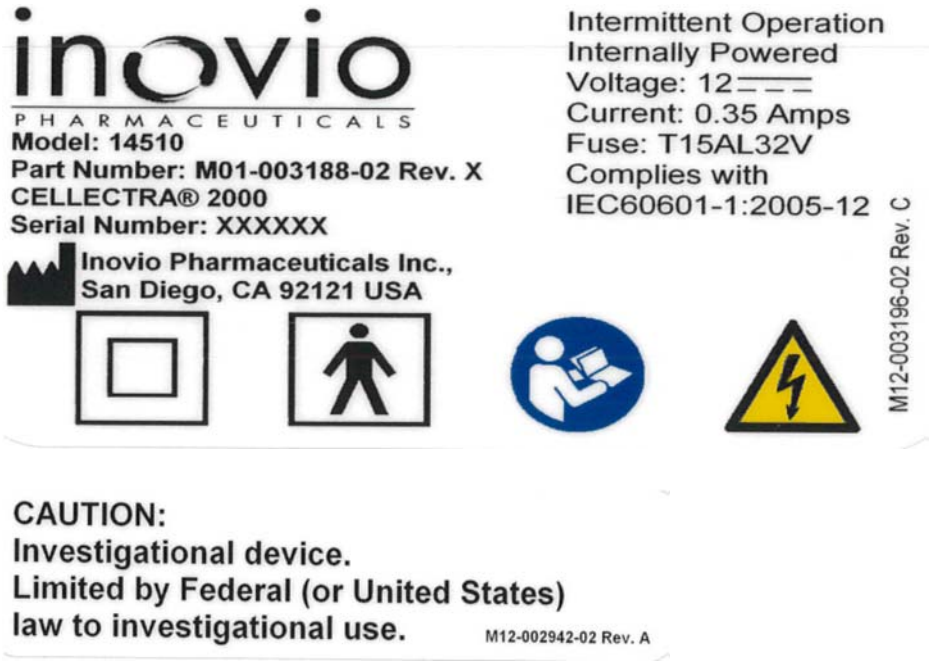
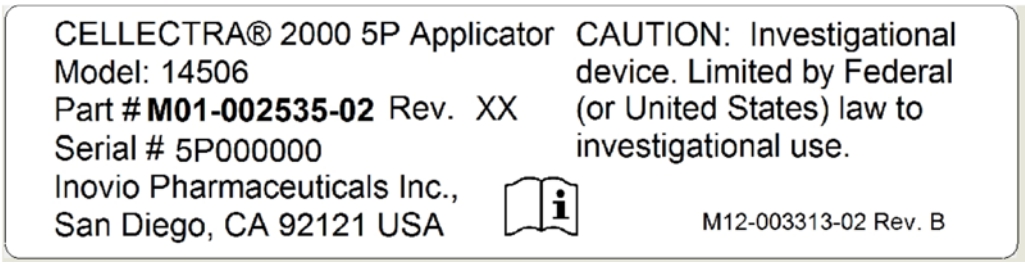
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform the procedure.

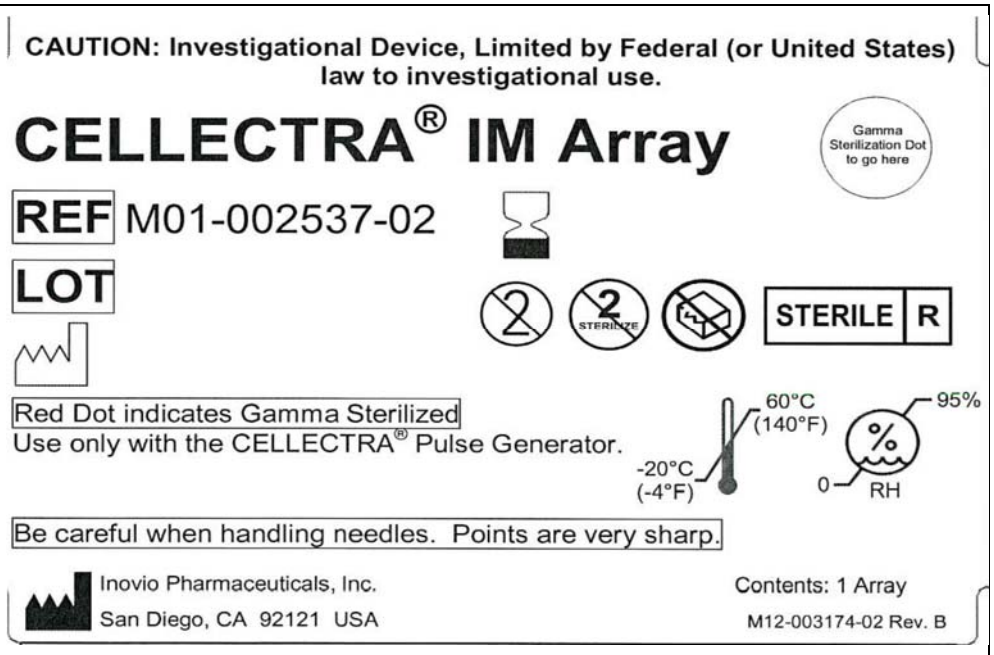
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA® 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 5 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 5. Example Labels for the CELLECTRA® 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA® 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA® 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA® IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA® 2000 serial number, applicator serial number, and array lot number. The CELLECTRA® 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. samples reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

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

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG (within 30 days prior to Day 0)
- Baseline laboratory evaluations (includes complete blood count [CBC), serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed within 30 days prior to Day 0
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Cervical cytology and ThinPrep™ for cervical HPV type
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected prior to and after biopsy at screening.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC. If residual vulvar tissue is available from entry either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria
- Review of concomitant medications and adverse events
- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- OP rinse, vaginal and intra-anal swabs
- Baseline vulvoscopy
- Vulvar lesion photography

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
  - After completing a review of PD 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.

6.2.3 WEEK 4

The following study evaluations will be performed at Week 4 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Targeted physical assessment

- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvoscopy
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12

The following study evaluations will be performed at Week 12 **prior to study treatment (± 7 days):**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvoscopy

- An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 and Week 94 unless PI suspects disease progression. All biopsy samples must be sent to the PAC for review
- Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression

- Vulvar Lesion Photography
  - Photographs of the vulva and the associated lesion must be collected.

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15

The following study evaluations will be performed at Week 15 (± 7 days):

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay including miRNA profile

6.2.7 WEEK 24

The following study evaluations will be performed at Week 24 **prior to study treatment (± 7 days)**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27

The following study evaluations will be performed at Week 27 (± 7 days):

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review
  - Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48

The following study evaluations will be performed at Week 48 (± 7 days):

- Targeted physical assessment

- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
  - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
  - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
  - All biopsy samples must be sent to the PAC for review
  - Slides from all excised tissue must be reviewed by the PAC
    - If residual vulvar tissue is available from entry and/or Week 48 specimen(s) either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18
- Patient Reported Outcomes

6.2.11 WEEK 52

Subjects will have a Week 52 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment

- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.12 WEEK 74

The following study evaluations will be performed at Week 74 (± 14 days):

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar lesion photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.13 WEEK 78

Subjects will have a Week 78 consultation (± 14 days) to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after** study treatment:

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.14 WEEK 96

The following study evaluations will be performed at Week 96 (± 14 days):

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical cytology and ThinPrep™ for HPV type
- OP oral rinse, vaginal and intra-anal swabs
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Vulvoscopy
    - Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression.
- Vulvar Lesion Photography
    - Photographs of the vulva and the associated lesion must be collected.
- Vulvar biopsy or wide excision as per investigator discretion:
    - All biopsy samples must be sent to the PAC for review
    - Slides from all excised tissue must be reviewed by the PAC

If residual vulvar tissue is available either paraffin blocks or unstained slides should be sent to the central pathology laboratory for IHC and testing for presence of HPV-16 and HPV-18

6.2.15 WEEK 100

The following study evaluations will be performed at Week 100 (± 14 days):

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.3 SAFETY EVALUATIONS

6.3.3.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). It will include an assessment of the following: general appearance, skin, head, eyes, ears, nose, and throat, and lymph nodes, and respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, and neurological systems.

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

6.3.3.2 VITAL SIGNS

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

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

6.3.3.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.3.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.3.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.3.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.3.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.3.8 ELECTROCARDIOGRAM (ECG)

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

6.3.3.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

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

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

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

6.3.3.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA® 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

No serious related adverse events to VGX-3100 have been observed in the clinical trial experience to date. A summary of potential risks of IM Administration followed by EP with CELLECTRA™ can be found in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

Adverse events reported in clinical trials with imiquimod cream, 5% for external genital warts can be found in the imiquimod product label [30], and in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO EP PROCEDURE

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

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at day 0, Weeks 4 and/or 12. Subjects who receive

a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.3.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. The following PRO questionnaires will be used:

1. **Short Form Health Survey, version 2 (SF-36v2™)** (Optum, Inc.): generically measures functional health and well-being, for physical and mental health; consists of thirty-six items covering eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) [31]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
2. **EQ-5D-5L** (EuroQol Research Foundation): generically measures activities & general health status; consists of six items covering six domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status) [32, 33] and will be administered as described below:

- Day 0 (*before* the first study treatment)
- 8-14 days post dose 1
- Week 4 (after study treatment)
- 8-14 days post dose 2
- Week 12 (after study treatment)
- Week 15
- Week 24 (after study treatment)
- Week 27
- Week 48 (after biopsy or surgical excision)
- Week 74 (after biopsy or surgical excision)
- Week 96 (after biopsy or surgical excision)
- Week 100

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.

3. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

Profiling of miRNA will occur using plasma obtained at Day 0, Week 15 and 48. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 and 48 samples will be done as a comparison against Day 0, in order to look for changes in miRNA profiles

that occur once dosing with VGX-3100 has begun, to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

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

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

A 4 mm vulvar punch biopsy sample will be obtained at Screening, Weeks 48, 74, and 96, and will be sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a 4 mm vulvar biopsy will be obtained from two regions of most advanced and severe disease as judged by the investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching vulvar biopsy samples to eliminate potential interference with the results of HPV testing.

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Screening and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep™ test kits at Screening, Weeks 27, 48, 74 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep™ specimen. At each of these visits, menstrual cycle status & recent history will be collected via self-report. If the Pap smear result suggests progression to cancer the investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Digital photographs

of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions which appears to have the highest likelihood according to the investigator of most advanced disease and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. An unscheduled biopsy may be performed at the discretion of the investigator if there is suspicion of disease progression. Guidelines for managing the findings of unscheduled biopsies for suspected disease progression are described in Table 7. Consult the Medical Monitor for any planned departures from these guidelines.

Table 7: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the investigator suspects disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the default "Schedule of Events", Table 1. Histologic samples and photographic documentation should be obtained for these cases.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

- Previous treatment with imiquimod for vulvar HSIL within 4 weeks prior to screening

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal demise, still birth, congenital anomaly of fetus/newborn); see Section 7.1.9 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

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

7.1.2 SERIOUS ADVERSE EVENTS

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

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

development of drug dependency or drug abuse or 4) the development of a malignancy;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

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

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 9.5.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of carcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility; i.e., there is evidence to suggest a causal relationship between the product and the adverse event. An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE

constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

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

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

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

- Requires therapeutic intervention or diagnostic tests

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

7.1.10 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 related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

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

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA® 2000 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
- Grade 3 or greater laboratory abnormalities

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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator, the DSMB, and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;

- Any subject experiences an SAE (or potentially life threatening AE) or death assessed as related to Study Treatment;
- Three or more subjects experience the same grade 3 or 4 adverse event, assessed as related to Study Treatment;
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to Study Treatment;

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.6 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.7 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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 as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify

regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.6 and 7.1.7).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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

Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

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

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of

the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and

percentages for categorical variables, by treatment arm, for the mITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are those that were used before the start of the trial (within 10 weeks prior to Day 0). Concomitant medications are those used during the course of the trial (on or after Day 0). Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) vulvoscopy 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 and treatment group as regressor variables.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and 95% Clopper-Pearson confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, 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.

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by the Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or

administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 three pathologists. Each specimen will be read by two pathologists independently in a masked fashion. If the two pathologists agree on the diagnosis then no further action is required and the clinical disease status for the subject will be established. If there is disagreement between the first two pathologists, the third pathologist will review and if there is agreement among any two of the three diagnoses, it will stand as the clinical disease status for that subject. If there is no agreement after the third review, the three reviewers will perform a simultaneous review and come to consensus or a majority rule of 2 of 3 if consensus cannot be reached.

10.4.3 CLINICAL MONITORING

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

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

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECC	Endocervical Curettage
EDC	Electronic Data Capture
EP	Electroporation with CELLECTRA® 2000
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HSIL	High grade squamous intraepithelial lesion
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular

IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response System
LAST	Lower Anogenital Squamous Terminology
MedDRA®	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified Intent to Treat
NILM	Negative for intraepithelial lesion or malignancy
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PCR	Polymerase Chain Reaction
PBMC	Peripheral Blood Mononuclear Cells
PD	Participant Diary
PRO	Patient Reported Outcomes
PE	Physical exam
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
SSC	Saline Sodium Citrate
sWFI	Sterile Water for Injection
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential

13. REFERENCES

1. Bruni L B-RL, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. Human Papillomavirus and Related Diseases in United States of America. Summary Report 2016-02-26. . In. Edited by Centre). IICoHaCHI; 2016.
2. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.
3. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.
4. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.
5. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.
6. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.
7. Sideri M JR, Wilkinson EJ, Preti M, Heller DS, Scurry J, Haefner H, Neill S. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.
8. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.
9. Inovio Pharmaceuticals. Unpublished assessment. 2015.
10. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.
11. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.
12. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.
13. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.
14. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.
15. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

16. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

17. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

18. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

19. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

20. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

21. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

22. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

23. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

24. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

25. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

26. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

27. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

28. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

29. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

30. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

31. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

32. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

33. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA™ 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #13683

Version 2.0
20 November 2017

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] _____

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

Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature:

_____ _____
Insert Principal Investigator Printed Name Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.3 dated 21 April 2017 to Version 2.0 dated 20 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. On the title page, U.S. BB has been removed from the IND number. The IND number remains the same.
2. To support enrollment, approximately 28 sites will be participating in the trial over the initially proposed 20 sites, and although not yet determined, the trial may potentially add countries outside of the United States.
3. Due to the possibility of adding countries outside of the United States, CELLECTRA® 2000 will use the trademark symbol, CELLECTRA™ 2000. This change has been made throughout the protocol.
4. Secondary Endpoint #4 have been modified to include no evidence of vulvar LSIL (VIN1), in addition to no evidence of vulvar HSIL and condyloma at Week 48 in the measurement of histologic regression of vulvar HSIL to normal tissue. Normal tissue is considered as no histologic evidence of vulvar LSIL, HSIL or condyloma.
5. Secondary Endpoint #6 and Exploratory Endpoint #1 have been modified to indicate that quantitative analysis will be determined from the pre-biopsy image of the qualifying lesion(s). A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee (PAC) at screening.
6. Exploratory Endpoint #4 will be evaluated by the assessment of pro-inflammatory and immunosuppressive elements in tissue, over the assessment of CD8+ and FoxP3 infiltrating cells for the immune tissue responses for VGX-3100 and VGX-3100 with imiquimod.
7. Exploratory Objective #8 has been updated to include the Week 15 and 27 time points for the administration of the Patient-Reported Outcomes (PROs) as it was inadvertently not included in version 1.3 dated 21 Apr 2017.
8. The WOMAN-PRO (WOMen with vulvAr Neoplasia) Clinical Trial Version 2.0 PRO instrument has been included in the protocol to assess both physical and psychosocial impacts of VIN and will be administered at the same time points as the EQ-5D-5L.
    - Section 1.1.15 was added to the protocol amendment to provide background information on the development of the WOMAN-PRO
    - Section 6.8 was updated to include the administration time points of the WOMAN-PRO
    - Section 12: List of abbreviations updated to include WOMAN-PRO
9. Section 1.1.1 and 1.1.2 modified to include European data of new cases diagnosed with HPV infection and vulvar cancer.
10. The requirement of a minimum 4 mm vulvar biopsy/biopsies has been replaced with a punch biopsy of approximately 4 mm in size in order to accommodate smaller lesions accessible by punch biopsy.

11. Repeat vulvar punch biopsies will be taken from the same qualifying lesion(s) as trial entry, but has been modified to clarify that the region of most advanced disease of the same lesion(s) will be obtained.
    - Table 2: Minimally required Procedure at Biopsy Visit has been updated to reflect the change
12. Inclusion/Exclusion criteria revised as follows:
    i. Inclusion Criteria #3: Revised to clarify that vulvar infection with HPV types 16 and/or 18 will be confirmed by screening biopsy. Subjects do not need to have a confirmed diagnosis of HPV-16 and/or 18 to participate in the study
    ii. Inclusion Criteria #4: Combined with previous inclusion criteria #5 as subjects must have a vulvar tissue specimen/blocks and histological confirmed vulvar HSIL from the Pathology Adjudication Committee at screening
    iii. Inclusion Criteria #6 (previously #7): Modified to accommodate smaller lesions accessible to punch biopsy
    iv. Inclusion Criteria #8b (previously 9b): Modified to include women who have had a bilateral tubal ligation/occlusion performed more than 3 months prior to screening. Tubal ligation is almost 100% effective for the prevention of pregnancy and thus subjects are not required to wait 12 months prior to screening to be eligible
    v. Exclusion Criteria #2, 3 and 4: Subjects who are under the care of a healthcare provider for their biopsy-proven VAIN, AIN, or CIN but may not be receiving active treatment are eligible for this trial. These criteria were modified in consideration of subjects who are under medical surveillance by their healthcare provider per standard of care
    vi. Exclusion Criteria #6 has been removed to avoid repetition as Inclusion Criteria # 4 states that the biopsy must be collected within 10 weeks prior to the anticipated 1st dose of the subject
    vii. Exclusion Criteria previously #9 and #10: Removed as it falls under the Exclusion Criteria #4 (Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN)
    viii. Exclusion Criteria #12 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 within 45 days prior to Day 0 to determine eligibility
    ix. Exclusion Criteria #15 has been modified to ensure that subjects do not receive live vaccines within 4 weeks of any of the scheduled doses
    x. Exclusion Criteria #16 has been modified to ensure that subjects do not receive any non-live vaccines within 2 weeks of any of the scheduled doses
    xi. Exclusion Criteria previously #22 to #27 now fall under the subgroup of exclusion criteria #18 and are numbered as #18a to #18g. These items include the list of exclusions that fall under the category of current or historically clinically significant, medically unstable disease

xii. Exclusion Criteria previously #22 (now #18b): Modified to ensure that only subjects with treatment of non-anogenital malignancy within 2 years of screening are excluded from the trial. Subjects in this population could be expected to have anogential malignancy within 2 years of study start which has been treated and therefore should not be excluded from trial participation
xiii. Exclusion Criteria previously #30 to #32 now fall under the subgroup of inclusion criteria 20 and numbered as #20a, #20b, and #20c accordingly. The sub group categorizes subjects with less than two acceptable sites for IM injection
xiv. Exclusion Criteria previously #33 to #36 now fall under the category of vulnerable populations and are numbered now #21a, #21b, #21c and #21d

13. The time points for cervical cytology and ThinPrep® have been changed and will be completed at Day 0 instead of at Screening as it is not required for study eligibility. The Week 27 cervical cytology and ThinPrep® has been moved to Week 12 to allow an earlier exploration for prediction of lesion regression from a dosed subject prior to the efficacy timepoint. The cervical cytology and ThinPrep® at Week 74 has been removed and all changes have been updated in the Schedule of Events.
14. Cervical colposcopy will be completed at Day 0 and Week 96 rather than Screening and Week 96 since cervical colposcopy is not required to determine eligibility on study. This change has been updated in the Schedule of Events.
15. Collection of vulvar swabs has been included in Exploratory Objective #7 and the Schedule of Events, to explore a potential new method for the detection of HPV in vulvar swabs. The collection will be completed at Day 0, Weeks 4, 12, 27, 48, 74 and 96.
16. Table 3: Definition of Responder and Non-Responder modified to include other treatments (e.g. surgical intervention) for vulvar HSIL treatment.
17. Figures 2, 3 and 4 of the protocol have been modified in Subgroup E to include subjects that have worsened to cancer and not limited to subjects that worsen from vulvar HSIL alone to cancer.
18. The screening assessments of 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis window has increased to 45 days prior to first dose administration. This was intended to allow subjects to complete trial procedures at their initial screening visit and avoid a second study visit for safety labs and/or ECG.
19. Immunohistochemistry (IHC) testing will not be performed for the detection of HPV-16 and/or HPV-18 in the trial. Sections throughout the protocol regarding ICH testing and in situ hybridization have been removed.
20. Section 5.4.2 (Dispensing and Use of Imiquimod) has been updated to have the Investigator contact the Medical Monitor to discuss alternative administration of imiquimod for subjects randomized to the imiquimod arm who cannot tolerate treatment.
21. Section 6.1 and 6.2 (Treatment Procedures) has been revised and updated to reflect the changes made on the removal and addition of treatment procedures in the Schedule of Events.
22. Section 6.3.2 (Rescreening of Screen Failures) has been added to allow rescreening of subjects after discussion with the Medical Monitor.

23. Section 6.4.2 (Management of Anxiety and Pain due to Electroporation procedure) has been modified to include Acetaminophen as an example of an analgesic to be provided to subjects. The language has been modified to include that the management may be offered before or after injection/EP.
24. Section 6.12 (Vulvar HPV Testing) additional language included in Section 6.12 as subjects will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of vulvar punch biopsy. This is intended to eliminate potential interference with the results of HPV testing.
25. Section 7.1.2 (Serious Adverse Events) has been revised to remove all redundancies in the section.
26. Section 7.3.1 (Adverse Events of Special Interest (AESI)) has been updated to remove Grade 3 or greater laboratory abnormalities as an AESI since safety labs are only drawn at screening and are not done after the administration of the investigational product VGX-3100.
27. Section 7.4.2 (Trial Reporting Period of Serious Adverse Events) and the Medical Monitor Approval Page has been updated to include the new HPV-201 Medical Monitor providing oversight of the trial.
28. Section 7.4.4 (Reporting of Device Related Complaints) has been updated to include an email address to report any device related complaints to the sponsor.
29. Section 8.3 (Sample Size/Power) modified to include the type of error level for each hypothesis.
30. Section 8.8 (Prior and Concomitant Medications) has been revised to the clearly define prior and concomitant medications.
31. Section 10.4.2 (Pathology Adjudication Committee) modified to remove procedural content in the protocol and refer to the PAC Charter.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA™ 2000 Alone or in Combination with Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 28 sites in the United States (US) and potentially other countries not yet determined	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3x) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related treatment for vulvar HSIL.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[6] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[7] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of qualifying**[8] **vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[8] lesion(s) at Week 48, 74 and 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.
[9] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[8] vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[8] lesion(s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit

[10] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[11] Additional assessments may include visualization of PD-L1, Granulysin, perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

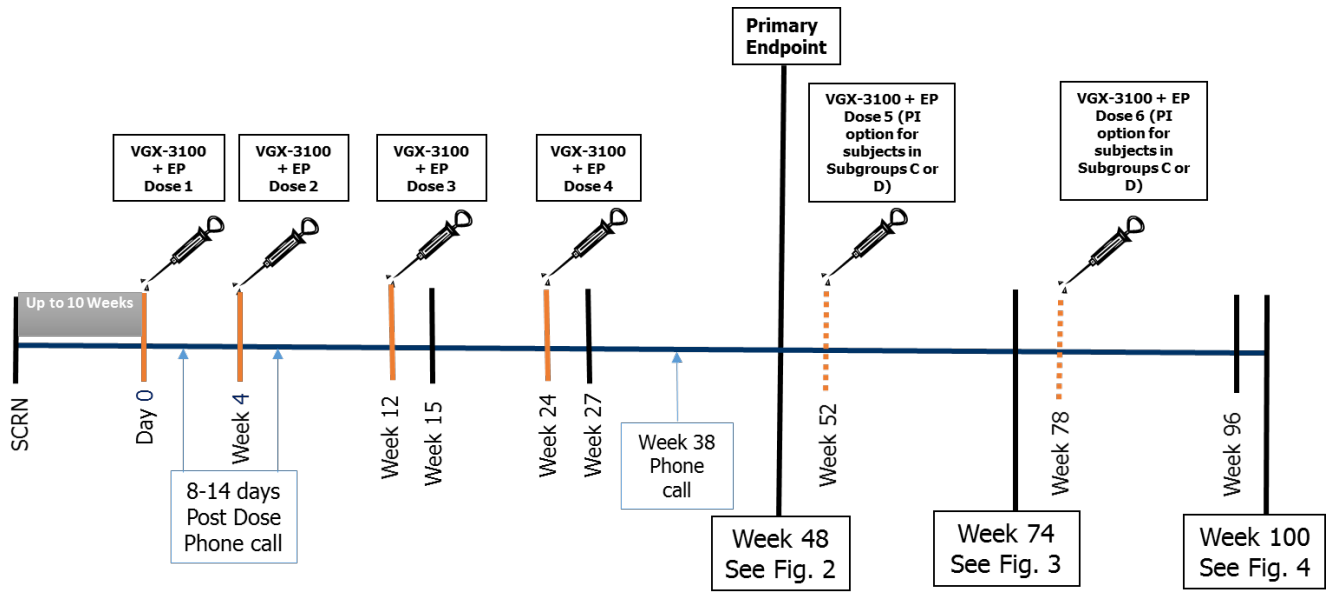
To be eligible for the study, subjects must consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera. Biopsy slides will be sent to the Pathology Adjudication Committee (PAC) by the central laboratory for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen 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 provided and will include the Short Form Health Survey version 2 (SF-36v2™) (Optum), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvAr Neoplasia) Clincial Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgment of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

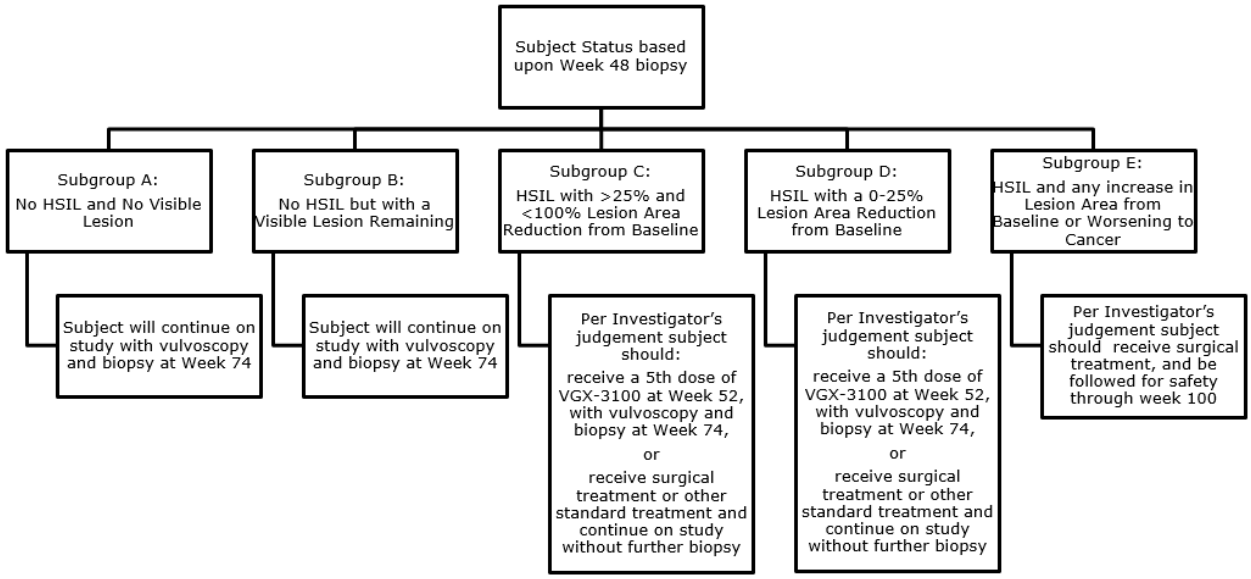
Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0 and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same lesion as study start.

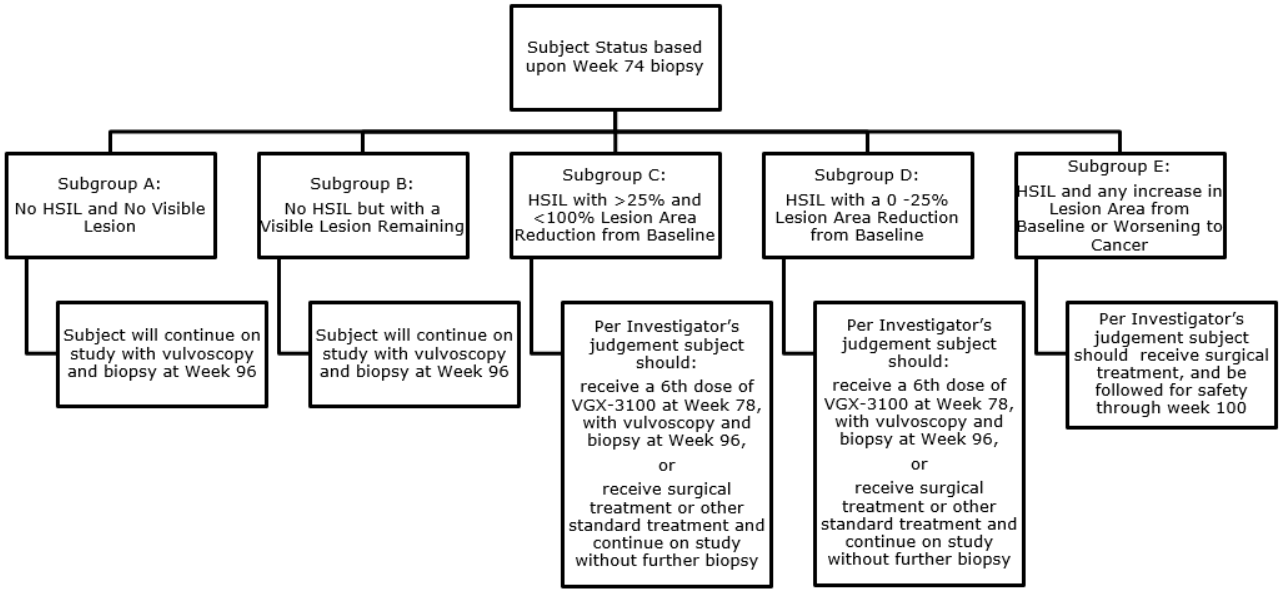
If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy. A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.

Figure 2: Decision process at Week 52



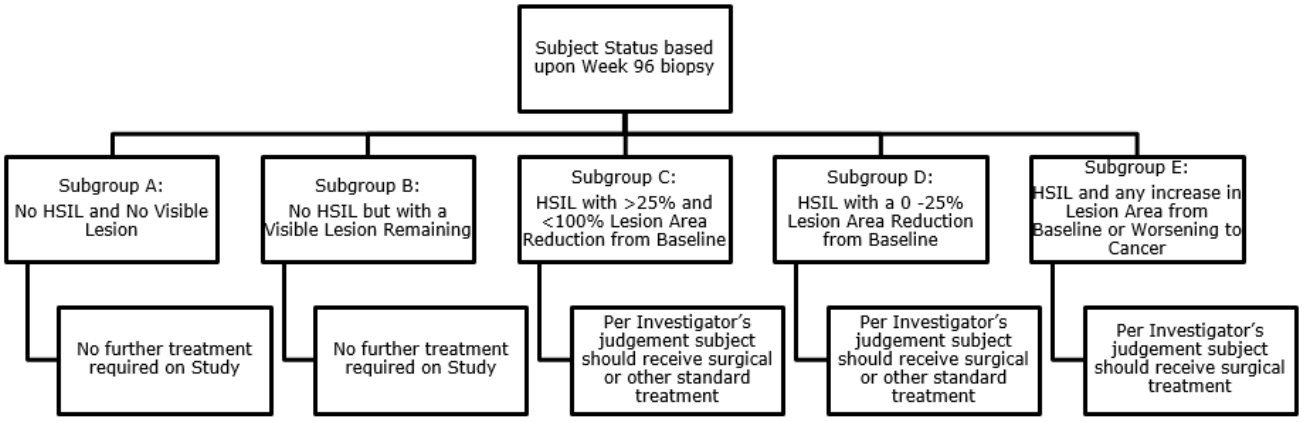
The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy of the same area from the region of potentially most advanced disease based upon the judgment of the Investigator. If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (i.e., Subgroup E – any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. If at any time in the study carcinoma is discovered, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

Data Safety & Monitoring Board (DSMB): The 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, Principal Investigator (PI) for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal rinse, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal). At Weeks 48 and 96, cervical sample will also be collected.

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c) Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8) Treatment for genital warts within 4 weeks prior to screening;
9) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
11) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12) 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;
13) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
15) Received any non-study related non-live vaccine within 2 weeks of each study dose;
16) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18) 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

c) 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;
d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
e) 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;
f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
g) Prior major surgery within 4 weeks of Day 0;

19) Participation in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
20) 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 (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);
21) Vulnerable populations:
    a) Active drug 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 service personnel who have the potential to be relocated;
    d) Study-related staff or family members of study-related staff;
22) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days)	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Socio-behavioral assessment	X										X					X
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]	X															
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Vulvar swabs		X		X		X			X		X		X		X	
Cervical colposcopy		X													X	
Cervical cytology, ThinPrep® [h]		X				X					X				X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [lm]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 45 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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. One additional 8.5 mL yellow (ACD) tube to be collected at Day 0, Week 15 and 48 for microRNA analysis.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep® cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Photography of the acetowhite stained qualifying lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at screening, a post biopsy photo will be sufficient. Additionally, standardized high resolution digital photographic imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) must be sent to the central pathology laboratory for HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36v2™, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16/18 is involved in about 83% of HPV-associated vulvar HSIL cases in the U.S. [1] and about 72% in Europe [2]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 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).

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 6,020 new cases and 1,150 attributable deaths annually for year 2017 in the United States [4] and about 9,776 new cases in 2015 in Europe [5]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [6]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 72.1% [4]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [7].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [8].

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which only high grade VIN (2/3) is classified as VIN [9]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [10]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, whichencompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [11]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [12], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [13].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates are as high as 45% at three years post-treatment with all currently available treatment regimens [14, 15].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk

of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [16].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [17]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [16]. Therefore, many patients have a fear of recurrence and progression to cancer [18].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid the use of toilet paper and to rinse with warm water instead. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [19]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [20].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [19]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [20].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [19].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid later development of HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [22]. However, these prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [23].

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan will be used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of subjects in this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study Investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists from the PAC (see Section 10.4.2). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible [24].

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.1). Colposcopy will also be performed at Day 0 and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out suspected disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgment.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [25, 26]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [27, 28]. 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 [29].

This study will use the CELLECTRA™ 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA™ 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV-16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [30].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Therefore, imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [17].

The current study will include an arm to explore whether the efficacy of VGX-3100 is able to be enhanced by concomitant treatment with Imiquimod.

1.1.15 INCLUSION OF WOMAN-PRO, CLINICAL TRIAL VERSION 2.0

The original WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) was developed by Beate Senn and colleagues [20,31,32] for use following post-surgical intervention. Development of the tool was aligned with the FDA PRO Guidance [33]and included a review of the literature as well as direct patient and expert input. Preliminary measurement properties were assessed in a cross-sectional study. However, despite rigorous development and promising initial measurement properties, gaps in the development and psychometric evaluation exist. To address these gaps, Inovio and collaborators initiated a small qualitative study to confirm the content validity of the tool and support a cross-cultural adaptation of the measure for use in a clinical trial setting of US English and US Spanish speaking subjects. The results of this research is the Clinical Trial of the WOMAN-PRO (2.0) which is utilized in this study.

The WOMAN-PRO Clinical Trial Version 2.0 is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The physical domain is comprised of 15 lesion-related symptoms and includes 5 additional items to measure impact in daily life. Psychosocial constructs are assessment through 11 items that address feelings, thoughts and limitations. Each item is scored using a 4-point Likert scale with higher scores indicating greater difficulty or severity. The recall period is the past week.Details are included in Section 6.8.

1.1.16 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been

reported at the application site [34]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.17 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[6] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of vulvar LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[7] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of the qualifying**[8] **vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[8] lesion (s) at Week 48, 74 and 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[8] vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[8] lesion (s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96 and 100.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

To be eligible for the study, subjects must sign consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides will be sent to a PAC for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen 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, PRO instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) Clinical Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid preferred site, or the anterolateral quadriceps as an alternate site) followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have

a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgment of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as at study start Investigator(see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy and biopsy of the same lesion as at study start. InvestigatorIf HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on

study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator. (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (i.e., Subgroup E - any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 2: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Acetowhite Lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Multiple acetowhite lesions	Vulvar punch biopsies and lesion photography; biopsy should be conducted of the same qualifying lesions as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology according to the PAC.

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

Table 3: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data and regression/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, 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 AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study

treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and Vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal only). At week 48 and 96, a cervical sample will also be collected.

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have confirmed histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of

adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;

7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c. Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8. Treatment for genital warts within 4 weeks prior to screening;
9. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within

4 weeks prior to screening;

10. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
11. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12. 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;
13. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
15. Received any non-study related non-live vaccine within 2 weeks of each study dose;
16. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18. 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
    c) 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;
    d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
    e) 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;

f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;

g) Prior major surgery within 4 weeks of Day 0;

19. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);

20. 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 (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);

21. Vulnerable populations:

    a) Active drug 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 service personnel who have the potential to be relocated;

    d) Study-related staff or family members of study-related staff;

22. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the

discretion of the Investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document.

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 VIN, 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 she 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 she 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 1). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study.
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon™) technology. The VGX-3100 formulation to be used in this study is described in Table 4 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 4. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. The actual product label names the product as VGX-3100X; the "X" designation was included to differentiate the current buffer formulation from a previous formulation of VGX-3100 in water. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL]

1 mL/Vial Single Use Vial

Date of Manufacture: _____

Expiry Date: _____

Refrigerate at 2-8°C

CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY

Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: Imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Ophthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours. In the event that Imiquimod is not tolerated at 3 times per week, alternative administration approaches must be discussed and approved by the medical monitor.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

5.7 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA™ 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA™ 2000 device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 Pulse Generator has a unique serial number, and each CELLECTRA™ 2000 Applicator has a unique serial number. Each CELLECTRA™ 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

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

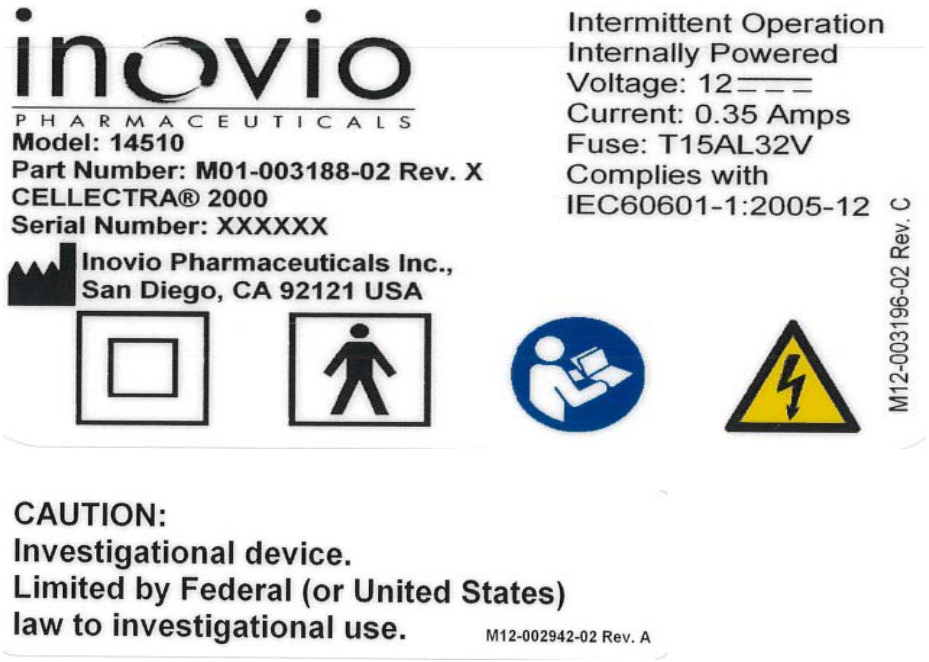
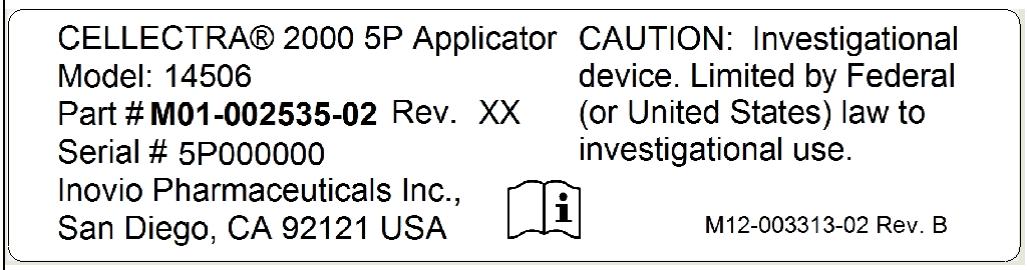
1. The procedure must be performed under the direct supervision of the Investigator or an approved Sub-Investigator who has already been trained by the sponsor's personnel.
2. The CV and any relevant qualifications of the individual must be reviewed and approved by the sponsor or its designee to perform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

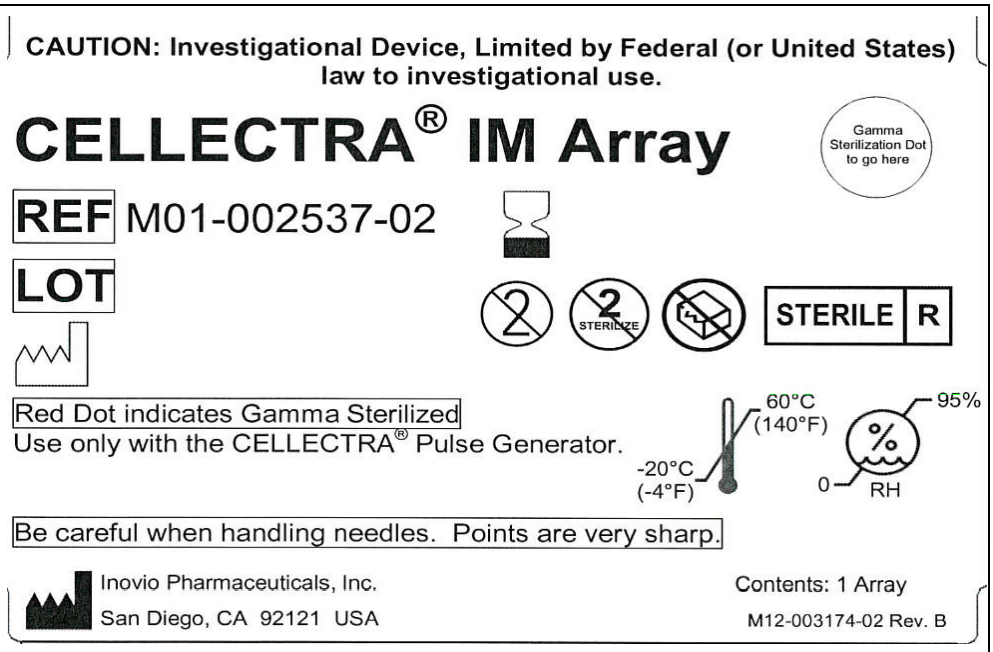
Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 5 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 5. Example Labels for the CELLECTRA™ 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA™ 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA™ 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA™ IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 2000 serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. samples reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

The following screening evaluations will be performed within 10 weeks and up to 1 day prior to dosing on Day 0, except for 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.

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG **(within 45 days prior to Day 0)**
- Baseline laboratory evaluations (includes complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed **within 45 days prior to Day 0**
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Vulvoscopy
  - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
  - Photograph of the vulvar lesion(s) must be collected prior to and after biopsy at screening
  - If a **historical biopsy** sample is used to determine eligibility at screening and a pre-biopsy photograph is not available, a post biopsy photo will be sufficient.
- Biopsy:
  - Slides from all excised tissue must be reviewed by the PAC.

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria
- Review of concomitant medications and adverse events

- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
    - After completing a review of PD 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.

6.2.3 WEEK 4 (± 7 DAYS):

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

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs

- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvar swab
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12 (± 7 DAYS)

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

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Cervical cytology and ThinPrep® for cervical HPV type
  - Collect menstrual cycle status and recent gynecologic history
- Vulvar swab
- Vulvoscopy

- Vulvar lesion photography of the qualifying lesion(s)

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15 (± 7 DAYS):

The following study evaluations will be performed at Week 15:

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay including miRNA profile

6.2.7 WEEK 24 (± 7 DAYS)

The following study evaluations will be performed at Week 24 **prior to study treatment**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27 (± 7 DAYS)

The following study evaluations will be performed at Week 27:

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48 (± 7 DAYS)

The following study evaluations will be performed at Week 48:

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review
- Patient Reported Outcomes

6.2.11 WEEK 52 (± 14 DAYS)

Subjects will have a Week 52 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.12 WEEK 74 (± 14 DAYS)

The following study evaluations will be performed at Week 74:

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:

- All biopsy samples must be sent to the PAC for review

6.2.13 WEEK 78 (± 14 DAYS)

Subjects will have a Week 78 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.14 WEEK 96 (± 14 DAYS)

The following study evaluations will be performed at Week 96:

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.15 WEEK 100 (± 14 DAYS)

The following study evaluations will be performed at Week 100:

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 RESCREENING OF SCREEN FAILURES

Subjects who sign the informed consent and are assigned a subject identification number (SID) but do not meet the eligibility criteria or fall outside of the screening window will be considered screen failures. If the Investigator believes rescreening is warranted, the Investigator must contact the medical monitor to discuss.

6.3.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique SID, which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for

any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.4 SAFETY EVALUATIONS

6.3.4.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). 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. 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.

6.3.4.2 VITAL SIGNS

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

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

6.3.4.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.4.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the Investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.4.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.4.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.4.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.4.8 ELECTROCARDIOGRAM (ECG)

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

6.3.4.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

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

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

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

6.3.4.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

No serious related adverse events to VGX-3100 have been observed in the clinical trial experience to date. A summary of potential risks of IM Administration followed by EP with CELLECTRA™ can be found in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

Adverse events reported in clinical trials with imiquimod cream, 5% for external genital warts can be found in the imiquimod product label [35], and in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURE

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

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

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.4.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. Administration of PRO instruments will be performed according to the validated or otherwise developed procedures and instructions of each respective instrument. The following PRO questionnaires will be used:

1. **WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) Clinical Trial Version – 2.0** (Beate Senn; version modified by Inovio Pharmaceuticals and RTI Health Solutions): is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The recall period is the past week.[20].

   The WOMAN-PRO will be administered on paper only and should be the **first PRO instrument administrated** (i.e. before all other PROs) at each of the following time points:

   - Day 0 (*before* the first study treatment)
   - 8-14 days post dose 1
   - Week 4 (after study treatment)
   - 8-14 days post dose 2
   - Week 12 (after study treatment)
   - Week 15

- Week 24 (after study treatment)
- Week 27
- Week 48 (after biopsy or surgical excision)
- Week 74 (after biopsy or surgical excision)
- Week 96 (after biopsy or surgical excision)
- Week 100

2. **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) [36]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
3. **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) [37, 38] and will be administered as described below:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)
    - Week 96 (after biopsy or surgical excision)
    - Week 100
4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered on paper at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

Profiling of miRNA will occur using plasma obtained at Day 0, Week 15 and 48. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 and 48 samples will be done as a comparison against Day 0, in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun, to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after HPV genotyping and histologic diagnoses have been rendered at Screening, Weeks 48, 74 and 96, then unstained slides and/or the relevant paraffin blocks may be collected for assessment of pro-inflammatory and immunosuppressive elements in tissue, where feasible. Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

At Screening, Weeks 48, 74, and 96, a vulvar punch biopsy sample of approximately 4 mm will be obtained and sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a vulvar biopsy of approximately 4 mm will be obtained from two lesions that potentially contain the most advanced disease as judged by the Investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching to eliminate potential interference with the results of HPV testing.

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

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Day 0 and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep® test kits at Day 0, Weeks 12, 48 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep® specimen. At each of these visits, menstrual cycle status & recent gynecologic history will be collected. If the Pap smear result suggests progression to cancer the Investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression. An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected.

Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions that potentially contain the most advanced disease as judged by the Investigator and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review. Investigator guidelines for managing the findings of

unscheduled biopsies for suspected disease progression are described in Table 7. Consult the Medical Monitor for any planned departures from these guidelines.

Table 7: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the Investigator suspects disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the Schedule of Events on Table 1. Histologic samples and photographic documentation should be obtained for these cases.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal demise, still birth, congenital anomaly of fetus/newborn); see Section 7.1.11 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

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

7.1.2 SERIOUS ADVERSE EVENTS

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

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

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.2.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of carcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

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

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

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

expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The Investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

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

7.1.10 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 related

to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

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

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 2000 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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and PI, the DSMB, and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE) or death assessed as related to Study Treatment;
- Three or more subjects experience the same grade 3 or 4 adverse event, assessed as related to Study Treatment;
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to Study Treatment;

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets serious criteria. If the AE is considered serious, the Investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.5 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.6 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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 as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the Investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating Investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.5 and 7.1.6).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability,

reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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.

All complaints must be sent to ClinicalComplaint@inovio.com. Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

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

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a)

recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control with a one-sided 0.025 type 1 error level for each hypothesis, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are considered those medications taken prior to the first dose of study drug (i.e., Day 0). Concomitant medications are those used on or after Day 0. Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated exact Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) vulvoscopy 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 and treatment group as regressor variables.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and exact Clopper-Pearson 95% confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

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

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

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

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the Investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 up to four pathologists. Each specimen will be read by two pathologists independently in a masked fashion. The responsibilities and membership structure of the PAC is outlined in the PAC Charter, including the reporting of results.

10.4.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.

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

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CPK	Creatine Phosphokinase
CRF	Case Report Forms
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSMB	Data & Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
HSIL	High grade squamous intraepithelial lesion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response Technology
LAST	Lower Anogenital Squamous Terminology
mITT	Modified Intent to Treat
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Participant Diary
PE	Physical exam

PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential
WOMAN-PRO	WOMen with vulvAr Neoplasia PRO

13. REFERENCES

1. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. . Human Papillomavirus and Related Diseases in USA., ICO Information Centre on HPV and Cancer (HPV Information Centre), Summary Report 30 June 2017. 2017.

2. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human Papillomavirus and Related Diseases in Europe. ICO Information Centre on HPV and Cancer (HPV Information Centre) Summary Report 30 June 2017. 2017.

3. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.

4. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.

5. Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjose S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. *Infect Agent Cancer* 2017,**12**:19.

6. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.

7. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.

8. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.

9. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J*, et al.* Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.

10. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.

11. Inovio Pharmaceuticals. Unpublished assessment. 2015.

12. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.

13. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.

14. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.

15. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.

16. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.

17. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

18. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

19. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

20. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

21. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

22. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

23. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

24. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

25. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

26. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

27. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

28. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

29. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

30. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

31. Senn B. Creating and Validating a Patient-Reported Outcome Instrument for Women with Vulvar Neoplasia after Surgical-Treatment - A Mixed-Methods Project, Institute of Nursing Science (INS) University of Basel, University Hospital Berne, Switzerland. 2012.

32. Senn B, Mueller MD, Hasenburg A, Blankenstein T, Kammermann B, Hartmann A*, et al.* Development of a postsurgical patient-reported outcome instrument for women with vulvar neoplasia. *Oncol Nurs Forum* 2012,**39**:E489-498.

33. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) CfBEaRC, Center for Devices and Radiological Health (CDRH). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. 2009.

34. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

35. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

36. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

37. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

38. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA™ 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #13683

Version 2.1
01 December 2017

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

[redacted]
Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature: _____

_____ _____
Print Name of Principal Investigator Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 1.3 dated 21 April 2017 to Version 2.1 dated 01 Dec 2017. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. On the title page, U.S. BB has been removed from the IND number. The IND number remains the same.
2. To support enrollment, approximately 28 sites will be participating in the trial over the initially proposed 20 sites, and although not yet determined, the trial may potentially add countries outside of the United States.
3. Due to the possibility of adding countries outside of the United States, CELLECTRA® 2000 will use the trademark symbol, CELLECTRA™ 2000. This change has been made throughout the protocol.
4. Secondary Endpoint #4 have been modified to include no evidence of vulvar LSIL (VIN1), in addition to no evidence of vulvar HSIL and condyloma at Week 48 in the measurement of histologic regression of vulvar HSIL to normal tissue. Normal tissue is considered as no histologic evidence of vulvar LSIL, HSIL or condyloma.
5. Secondary Endpoint #6 and Exploratory Endpoint #1 have been modified to indicate that quantitative analysis will be determined from the pre-biopsy image of the qualifying lesion(s). A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee (PAC) at screening.
6. Exploratory Endpoint #4 will be evaluated by the assessment of pro-inflammatory and immunosuppressive elements in tissue, over the assessment of CD8+ and FoxP3 infiltrating cells for the immune tissue responses for VGX-3100 and VGX-3100 with imiquimod.
7. Exploratory Objective #8 has been updated to include the Week 15 and 27 time points for the administration of the Patient-Reported Outcomes (PROs) as it was inadvertently not included in version 1.3 dated 21 Apr 2017.
8. The WOMAN-PRO (WOMen with vulvAr Neoplasia) Clinical Trial Version 2.0 PRO instrument has been included in the protocol to assess both physical and psychosocial impacts of VIN and will be administered at the same time points as the EQ-5D-5L.
    - Section 1.1.15 was added to the protocol amendment to provide background information on the development of the WOMAN-PRO
    - Section 6.8 was updated to include the administration time points of the WOMAN-PRO
    - Section 12: List of abbreviations updated to include WOMAN-PRO
9. Section 1.1.1 and 1.1.2 modified to include European data of new cases diagnosed with HPV infection and vulvar cancer.
10. The requirement of a minimum 4 mm vulvar biopsy/biopsies has been replaced with a punch biopsy of approximately 4 mm in size in order to accommodate smaller lesions accessible by punch biopsy.

11. Repeat vulvar punch biopsies will be taken from the same qualifying lesion(s) as trial entry, but has been modified to clarify that the region of most advanced disease of the same lesion(s) will be obtained.
    - Table 2: Minimally required Procedure at Biopsy Visit has been updated to reflect the change
12. Inclusion/Exclusion criteria revised as follows:
    i. Inclusion Criteria #3: Revised to clarify that vulvar infection with HPV types 16 and/or 18 will be confirmed by screening biopsy. Subjects do not need to have a confirmed diagnosis of HPV-16 and/or 18 to participate in the study
    ii. Inclusion Criteria #4: Combined with previous inclusion criteria #5 as subjects must have a vulvar tissue specimen/blocks and histological confirmed vulvar HSIL from the Pathology Adjudication Committee at screening
    iii. Inclusion Criteria #6 (previously #7): Modified to accommodate smaller lesions accessible to punch biopsy
    iv. Inclusion Criteria #8b (previously 9b): Modified to include women who have had a bilateral tubal ligation/occlusion performed more than 3 months prior to screening. Tubal ligation is almost 100% effective for the prevention of pregnancy and thus subjects are not required to wait 12 months prior to screening to be eligible
    v. Exclusion Criteria #2, 3 and 4: Subjects who are under the care of a healthcare provider for their biopsy-proven VAIN, AIN, or CIN but may not be receiving active treatment are eligible for this trial. These criteria were modified in consideration of subjects who are under medical surveillance by their healthcare provider per standard of care
    vi. Exclusion Criteria #6 has been removed to avoid repetition as Inclusion Criteria # 4 states that the biopsy must be collected within 10 weeks prior to the anticipated 1st dose of the subject
    vii. Exclusion Criteria previously #9 and #10: Removed as it falls under the Exclusion Criteria #4 (Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN)
    viii. Exclusion Criteria #12 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 within 45 days prior to Day 0 to determine eligibility
    ix. Exclusion Criteria #15 has been modified to ensure that subjects do not receive live vaccines within 4 weeks of any of the scheduled doses
    x. Exclusion Criteria #16 has been modified to ensure that subjects do not receive any non-live vaccines within 2 weeks of any of the scheduled doses
    xi. Exclusion Criteria previously #22 to #27 now fall under the subgroup of exclusion criteria #18 and are numbered as #18a to #18g. These items include the list of exclusions that fall under the category of current or historically clinically significant, medically unstable disease

xii. Exclusion Criteria previously #22 (now #18b): Modified to ensure that only subjects with treatment of non-anogenital malignancy within 2 years of screening are excluded from the trial. Subjects in this population could be expected to have anogential malignancy within 2 years of study start which has been treated and therefore should not be excluded from trial participation
xiii. Exclusion Criteria previously #30 to #32 now fall under the subgroup of inclusion criteria 20 and numbered as #20a, #20b, and #20c accordingly. The sub group categorizes subjects with less than two acceptable sites for IM injection
xiv. Exclusion Criteria previously #33 to #36 now fall under the category of vulnerable populations and are numbered now #21a, #21b, #21c and #21d

13. The time points for cervical cytology and ThinPrep® have been changed and will be completed at Day 0 instead of at Screening as it is not required for study eligibility. The Week 27 cervical cytology and ThinPrep® has been moved to Week 12 to allow an earlier exploration for prediction of lesion regression from a dosed subject prior to the efficacy timepoint. The cervical cytology and ThinPrep® at Week 74 has been removed and all changes have been updated in the Schedule of Events.
14. Cervical colposcopy will be completed at Day 0 and Week 96 rather than Screening and Week 96 since cervical colposcopy is not required to determine eligibility on study. This change has been updated in the Schedule of Events.
15. Collection of vulvar swabs has been included in Exploratory Objective #7 and the Schedule of Events, to explore a potential new method for the detection of HPV in vulvar swabs. The collection will be completed at Day 0, Weeks 4, 12, 27, 48, 74 and 96.
16. Table 3: Definition of Responder and Non-Responder modified to include other treatments (e.g. surgical intervention) for vulvar HSIL treatment.
17. Figures 2, 3 and 4 of the protocol have been modified in Subgroup E to include subjects that have worsened to cancer and not limited to subjects that worsen from vulvar HSIL alone to cancer.
18. The screening assessments of 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis window has increased to 45 days prior to first dose administration. This was intended to allow subjects to complete trial procedures at their initial screening visit and avoid a second study visit for safety labs and/or ECG.
19. Immunohistochemistry (IHC) testing will not be performed for the detection of HPV-16 and/or HPV-18 in the trial. Sections throughout the protocol regarding IHC testing and in situ hybridization have been removed.
20. Section 5.4.2 (Dispensing and Use of Imiquimod) has been updated to have the Investigator contact the Medical Monitor to discuss alternative administration of imiquimod for subjects randomized to the imiquimod arm who cannot tolerate treatment.
21. Section 5.7 (Use of Investigational Device) has been modified to remove the allowance for individuals whose credentials do not meet the local requirements to administer treatment to subjects on the study. Treatment must be performed by qualified personnel whose credentials meet local requirements to administer parenteral injections.

22. Section 6.1 and 6.2 (Treatment Procedures) has been revised and updated to reflect the changes made on the removal and addition of treatment procedures in the Schedule of Events.
23. Section 6.3.2 (Rescreening of Screen Failures) has been added to allow rescreening of subjects after discussion with the Medical Monitor.
24. Section 6.4.2 (Management of Anxiety and Pain due to Electroporation procedure) has been modified to include Acetaminophen as an example of an analgesic to be provided to subjects. The language has been modified to include that the management may be offered before or after injection/EP.
25. Section 6.12 (Vulvar HPV Testing) additional language included in Section 6.12 as subjects will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of vulvar punch biopsy. This is intended to eliminate potential interference with the results of HPV testing.
26. Section 7.1.2 (Serious Adverse Events) has been revised to remove all redundancies in the section.
27. Section 7.3.1 (Adverse Events of Special Interest (AESI)) has been updated to remove Grade 3 or greater laboratory abnormalities as an AESI since safety labs are only drawn at screening and are not done after the administration of the investigational product VGX-3100.
28. Section 7.4.2 (Trial Reporting Period of Serious Adverse Events) and the Medical Monitor Approval Page has been updated to include the new HPV-201 Medical Monitor providing oversight of the trial.
29. Section 7.4.4 (Reporting of Device Related Complaints) has been updated to include an email address to report any device related complaints to the sponsor.
30. Section 8.3 (Sample Size/Power) modified to include the type of error level for each hypothesis.
31. Section 8.8 (Prior and Concomitant Medications) has been revised to the clearly define prior and concomitant medications.
32. Section 10.4.2 (Pathology Adjudication Committee) modified to remove procedural content in the protocol and refer to the PAC Charter.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA™ 2000 Alone or in Combination with Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 28 sites in the United States (US) and potentially other countries not yet determined	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3x) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36 subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[3] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[4]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[4] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related treatment for vulvar HSIL.

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[6] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[7] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of qualifying**[8] **vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[8] lesion(s) at Week 48, 74 and 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma
[6] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[7] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
[8] A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.
[9] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[8] vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[8] lesion(s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit

[10] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[11] Additional assessments may include visualization of PD-L1, Granulysin, perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

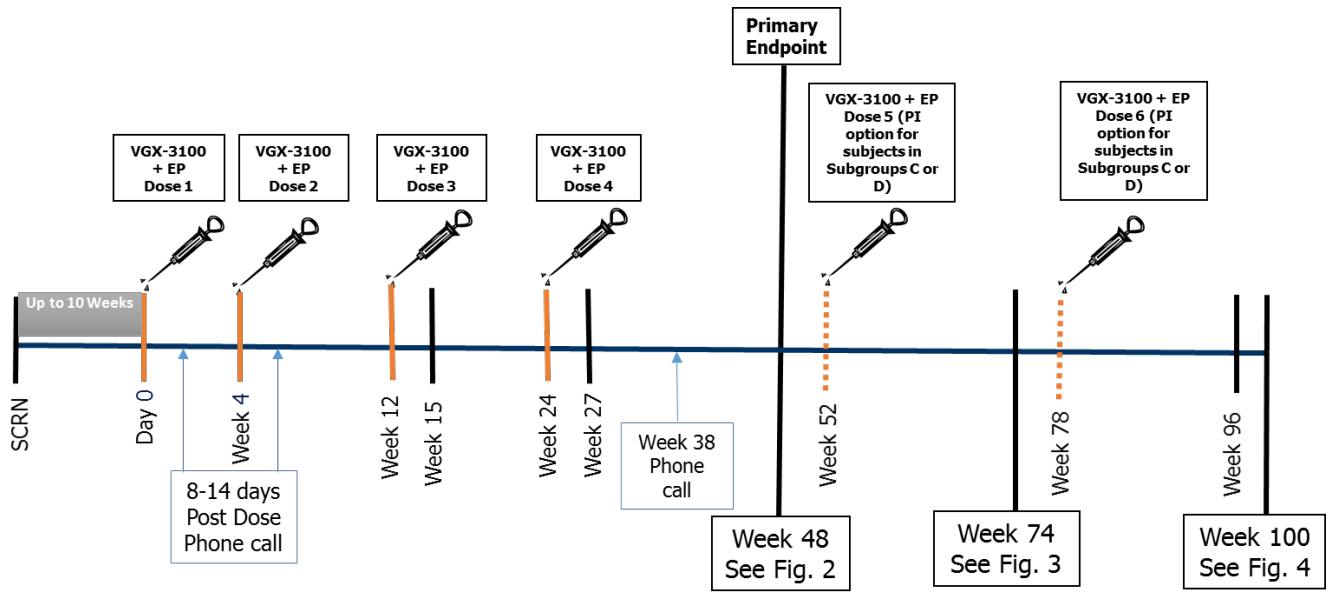
To be eligible for the study, subjects must consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera. Biopsy slides will be sent to the Pathology Adjudication Committee (PAC) by the central laboratory for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen 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 provided and will include the Short Form Health Survey version 2 (SF-36v2™) (Optum), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvAr Neoplasia) Clincial Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgment of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

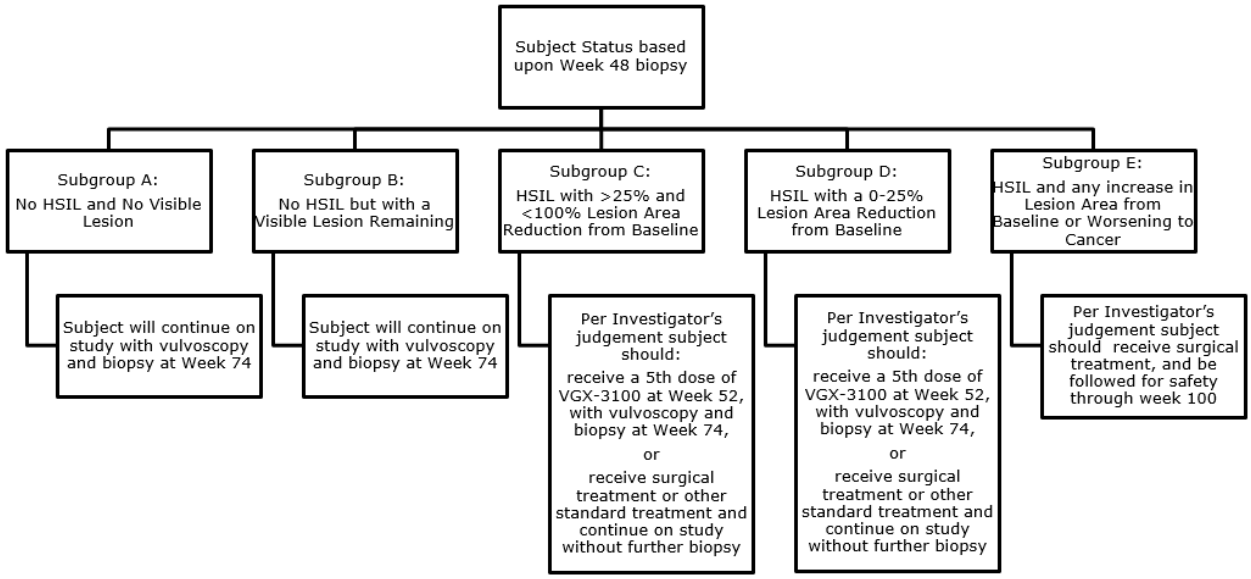
Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0 and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same lesion as study start.

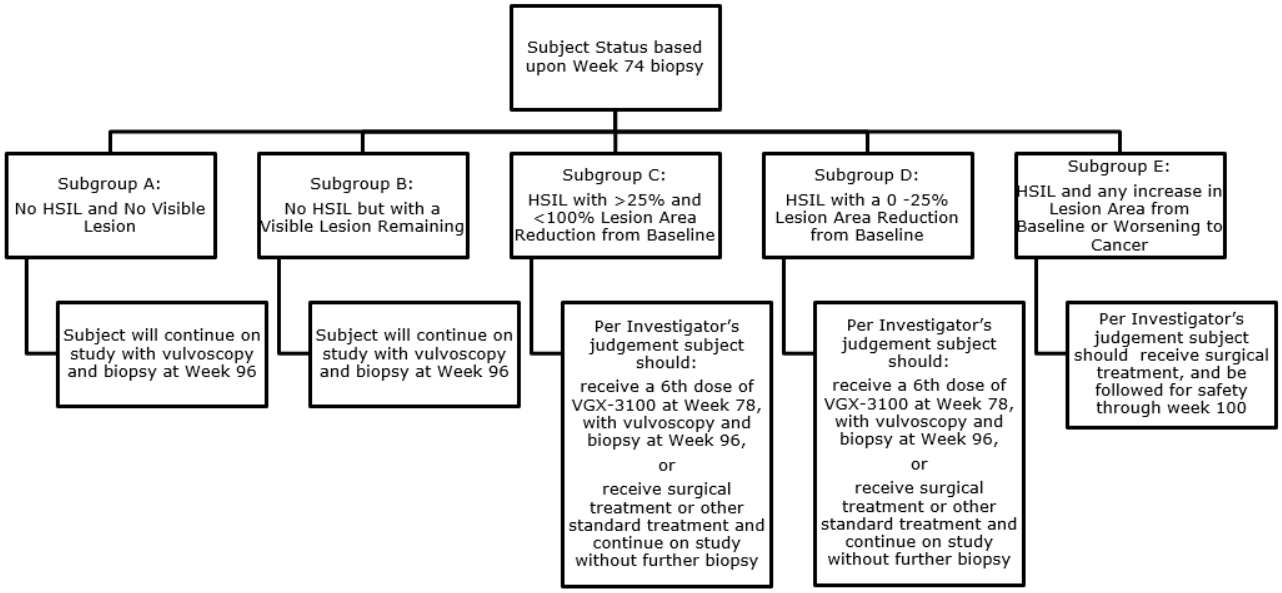
If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy. A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.

Figure 2: Decision process at Week 52



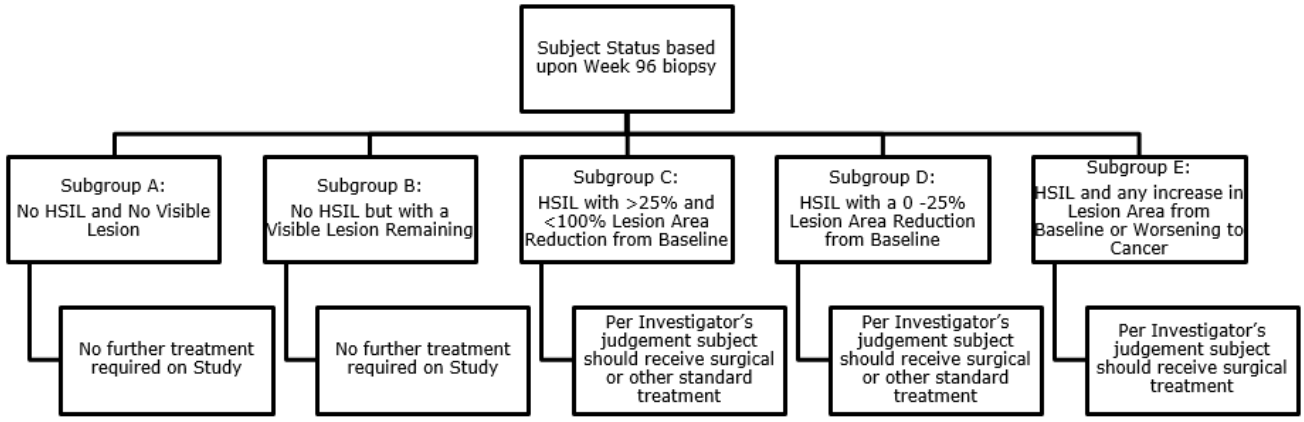
The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy of the same area from the region of potentially most advanced disease based upon the judgment of the Investigator. If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (i.e., Subgroup E – any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. If at any time in the study carcinoma is discovered, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

Data Safety & Monitoring Board (DSMB): The 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, Principal Investigator (PI) for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal rinse, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal). At Weeks 48 and 96, cervical sample will also be collected.

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c) Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8) Treatment for genital warts within 4 weeks prior to screening;
9) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
11) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12) 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;
13) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
15) Received any non-study related non-live vaccine within 2 weeks of each study dose;
16) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18) 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

c) 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;
d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
e) 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;
f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
g) Prior major surgery within 4 weeks of Day 0;

19) Participation in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
20) 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 (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);
21) Vulnerable populations:
    a) Active drug 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 service personnel who have the potential to be relocated;
    d) Study-related staff or family members of study-related staff;
22) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days)	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Socio-behavioral assessment	X										X					X
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]	X															
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Vulvar swabs		X		X		X			X		X		X		X	
Cervical colposcopy		X													X	
Cervical cytology, ThinPrep® [h]		X				X					X				X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [lm]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 45 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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. One additional 8.5 mL yellow (ACD) tube to be collected at Day 0, Week 15 and 48 for microRNA analysis.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep® cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Photography of the acetowhite stained qualifying lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at screening, a post biopsy photo will be sufficient. Additionally, standardized high resolution digital photographic imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) must be sent to the central pathology laboratory for HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36v2™, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16/18 is involved in about 83% of HPV-associated vulvar HSIL cases in the U.S. [1] and about 72% in Europe [2]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 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).

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 6,020 new cases and 1,150 attributable deaths annually for year 2017 in the United States [4] and about 9,776 new cases in 2015 in Europe [5]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [6]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 72.1% [4]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [7].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [8].

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which only high grade VIN (2/3) is classified as VIN [9]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [10]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, whichencompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [11]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [12], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [13].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates are as high as 45% at three years post-treatment with all currently available treatment regimens [14, 15].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk

of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [16].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [17]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [16]. Therefore, many patients have a fear of recurrence and progression to cancer [18].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid the use of toilet paper and to rinse with warm water instead. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [19]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [20].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [19]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [20].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [19].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid later development of HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [22]. However, these prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [23].

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan will be used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of subjects in this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study Investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists from the PAC (see Section 10.4.2). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible [24].

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.1). Colposcopy will also be performed at Day 0 and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out suspected disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgment.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [25, 26]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [27, 28]. 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 [29].

This study will use the CELLECTRA™ 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA™ 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV-16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration arm is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [30].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Therefore, imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [17].

The current study will include an arm to explore whether the efficacy of VGX-3100 is able to be enhanced by concomitant treatment with Imiquimod.

1.1.15 INCLUSION OF WOMAN-PRO, CLINICAL TRIAL VERSION 2.0

The original WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) was developed by Beate Senn and colleagues [20,31,32] for use following post-surgical intervention. Development of the tool was aligned with the FDA PRO Guidance [33]and included a review of the literature as well as direct patient and expert input. Preliminary measurement properties were assessed in a cross-sectional study. However, despite rigorous development and promising initial measurement properties, gaps in the development and psychometric evaluation exist. To address these gaps, Inovio and collaborators initiated a small qualitative study to confirm the content validity of the tool and support a cross-cultural adaptation of the measure for use in a clinical trial setting of US English and US Spanish speaking subjects. The results of this research is the Clinical Trial of the WOMAN-PRO (2.0) which is utilized in this study.

The WOMAN-PRO Clinical Trial Version 2.0 is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The physical domain is comprised of 15 lesion-related symptoms and includes 5 additional items to measure impact in daily life. Psychosocial constructs are assessment through 11 items that address feelings, thoughts and limitations. Each item is scored using a 4-point Likert scale with higher scores indicating greater difficulty or severity. The recall period is the past week.Details are included in Section 6.8.

1.1.16 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been

reported at the application site [34]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.17 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[6] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of vulvar LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[7] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of the qualifying**[8] **vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[8] lesion (s) at Week 48, 74 and 96 compared to baseline[9]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[8] vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[8] lesion (s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96 and 100.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

To be eligible for the study, subjects must sign consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides will be sent to a PAC for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen 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, PRO instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) Clinical Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid preferred site, or the anterolateral quadriceps as an alternate site) followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5^{th} and 6^{th} dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have

a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgment of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod arm will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as at study start Investigator(see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy and biopsy of the same lesion as at study start. InvestigatorIf HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on

study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator. (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (i.e., Subgroup E - any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 2: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Acetowhite Lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Multiple acetowhite lesions	Vulvar punch biopsies and lesion photography; biopsy should be conducted of the same qualifying lesions as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology according to the PAC.

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

Table 3: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data and regression/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, 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 AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study

treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and Vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal only). At week 48 and 96, a cervical sample will also be collected.

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have confirmed histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of

adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;

7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c. Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8. Treatment for genital warts within 4 weeks prior to screening;
9. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within

4 weeks prior to screening;

10. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream;
11. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12. 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;
13. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
15. Received any non-study related non-live vaccine within 2 weeks of each study dose;
16. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18. 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
    c) 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;
    d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
    e) 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;

f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;

g) Prior major surgery within 4 weeks of Day 0;

19. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);

20. 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 (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);

21. Vulnerable populations:

    a) Active drug 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 service personnel who have the potential to be relocated;

    d) Study-related staff or family members of study-related staff;

22. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the

discretion of the Investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document.

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 VIN, 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 she 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 she 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 1). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study.
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon™) technology. The VGX-3100 formulation to be used in this study is described in Table 4 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 4. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. The actual product label names the product as VGX-3100X; the "X" designation was included to differentiate the current buffer formulation from a previous formulation of VGX-3100 in water. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL]

1 mL/Vial Single Use Vial

Date of Manufacture: _____

Expiry Date: _____

Refrigerate at 2-8°C

CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY

Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: Imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Ophthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours. In the event that Imiquimod is not tolerated at 3 times per week, alternative administration approaches must be discussed and approved by the medical monitor.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

5.7 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA™ 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA™ 2000 device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

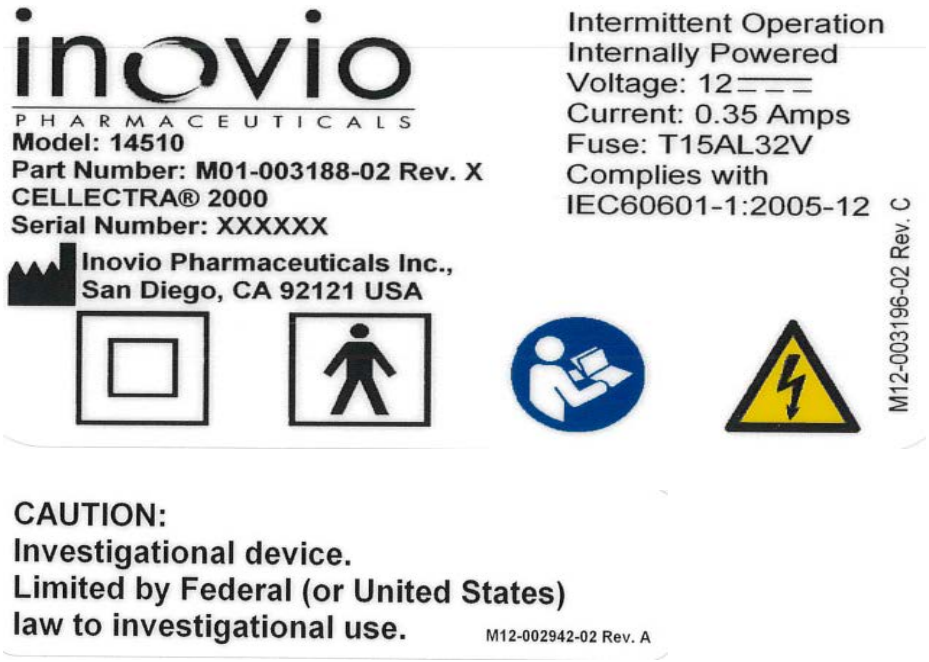
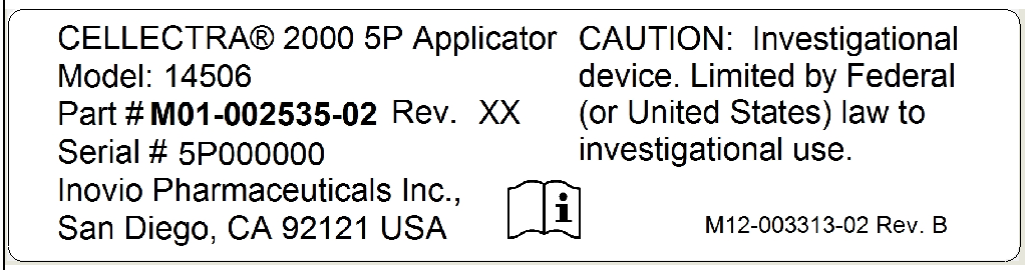
The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 Pulse Generator has a unique serial number, and each CELLECTRA™ 2000 Applicator has a unique serial number. Each CELLECTRA™ 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

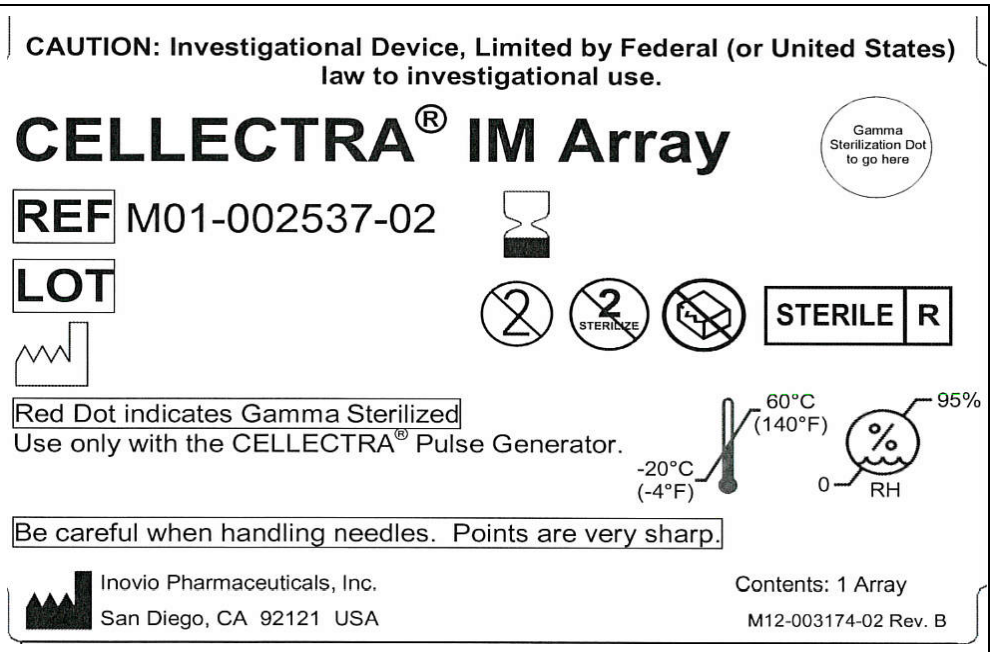
The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 5 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 5. Example Labels for the CELLECTRA™ 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA™ 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA™ 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA™ IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 2000 serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

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

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

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

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. samples reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

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

The following screening evaluations will be performed within 10 weeks and up to 1 day prior to dosing on Day 0, except for 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.

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG **within 45 days prior to Day 0**
- Baseline laboratory evaluations (includes complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed **within 45 days prior to Day 0**
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photograph of the vulvar lesion(s) must be collected prior to and after biopsy at screening
    - If a **historical biopsy** sample is used to determine eligibility at screening and a pre-biopsy photograph is not available, a post biopsy photo will be sufficient.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC.

6.2 DURING TREATMENT PROCEDURES BY VISIT

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

6.2.1 DAY 0

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

- Determination of eligibility per Inclusion/Exclusion Criteria
- Review of concomitant medications and adverse events

- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
    - After completing a review of PD 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.

6.2.3 WEEK 4 (± 7 DAYS)

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

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs

- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvar swab
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

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

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12 (± 7 DAYS)

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

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Cervical cytology and ThinPrep® for cervical HPV type
  - Collect menstrual cycle status and recent gynecologic history
- Vulvar swab
- Vulvoscopy

- Vulvar lesion photography of the qualifying lesion(s)

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

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15 (± 7 DAYS)

The following study evaluations will be performed at Week 15:

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay including miRNA profile

6.2.7 WEEK 24 (± 7 DAYS)

The following study evaluations will be performed at Week 24 **prior to study treatment**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27 (± 7 DAYS)

The following study evaluations will be performed at Week 27:

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48 (± 7 DAYS)

The following study evaluations will be performed at Week 48:

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.11 PATIENT REPORTED OUTCOMESWEEK 52 (± 14 DAYS)

Subjects will have a Week 52 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.12 WEEK 74 (± 14 DAYS)

The following study evaluations will be performed at Week 74:

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.13 WEEK 78 (± 14 DAYS)

Subjects will have a Week 78 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.14 WEEK 96 (± 14 DAYS)

The following study evaluations will be performed at Week 96:

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabsVulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.15 WEEK 100 (± 14 DAYS)

The following study evaluations will be performed at Week 100:

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

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

6.3.2 RESCREENING OF SCREEN FAILURES

Subjects who sign the informed consent and are assigned a subject identification number (SID) but do not meet the eligibility criteria or fall outside of the screening window will be considered screen failures. If the Investigator believes rescreening is warranted, the Investigator must contact the medical monitor to discuss.

6.3.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique SID, which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

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

6.3.4 SAFETY EVALUATIONS

6.3.4.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). 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. 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.

6.3.4.2 VITAL SIGNS

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

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

6.3.4.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.4.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the Investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.4.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.4.6 LABORATORY EVALUATIONS

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

Complete blood count (CBC):

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

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

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

6.3.4.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.4.8 ELECTROCARDIOGRAM (ECG)

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

6.3.4.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

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

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell

- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

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

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

6.3.4.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

No serious related adverse events to VGX-3100 have been observed in the clinical trial experience to date. A summary of potential risks of IM Administration followed by EP with CELLECTRA™ can be found in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

Adverse events reported in clinical trials with imiquimod cream, 5% for external genital warts can be found in the imiquimod product label [35], and in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURE

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an

approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

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

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

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

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.4.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

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

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

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

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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. Administration of PRO instruments will be performed according to the validated or otherwise developed procedures and instructions of each respective instrument. The following PRO questionnaires will be used:

1. **WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) Clinical Trial Version – 2.0** (Beate Senn; version modified by Inovio Pharmaceuticals and RTI Health Solutions): is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The recall period is the past week.[20].

   The WOMAN-PRO will be administered on paper only and should be the **first PRO instrument administrated** (i.e. before all other PROs) at each of the following time points:

   - Day 0 (*before* the first study treatment)
   - 8-14 days post dose 1
   - Week 4 (after study treatment)
   - 8-14 days post dose 2
   - Week 12 (after study treatment)
   - Week 15

- Week 24 (after study treatment)
- Week 27
- Week 48 (after biopsy or surgical excision)
- Week 74 (after biopsy or surgical excision)
- Week 96 (after biopsy or surgical excision)
- Week 100

2. **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) [36]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
3. **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) [37, 38] and will be administered as described below:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)
    - Week 96 (after biopsy or surgical excision)
    - Week 100
4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered on paper at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

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

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

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

Profiling of miRNA will occur using plasma obtained at Day 0, Week 15 and 48. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 and 48 samples will be done as a comparison against Day 0, in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun, to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after HPV genotyping and histologic diagnoses have been rendered at Screening, Weeks 48, 74 and 96, then unstained slides and/or the relevant paraffin blocks may be collected for assessment of pro-inflammatory and immunosuppressive elements in tissue, where feasible. Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

At Screening, Weeks 48, 74, and 96, a vulvar punch biopsy sample of approximately 4 mm will be obtained and sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a vulvar biopsy of approximately 4 mm will be obtained from two lesions that potentially contain the most advanced disease as judged by the Investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching to eliminate potential interference with the results of HPV testing.

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

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Day 0 and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep® test kits at Day 0, Weeks 12, 48 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep® specimen. At each of these visits, menstrual cycle status & recent gynecologic history will be collected. If the Pap smear result suggests progression to cancer the Investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

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

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression. An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected.

Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions that potentially contain the most advanced disease as judged by the Investigator and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review. Investigator guidelines for managing the findings of

unscheduled biopsies for suspected disease progression are described in Table 7. Consult the Medical Monitor for any planned departures from these guidelines.

Table 7: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the Investigator suspects disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the Schedule of Events on Table 1. Histologic samples and photographic documentation should be obtained for these cases.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

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

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

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

6.16.1 OTHER RESTRICTIONS

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

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

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

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

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

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal demise, still birth, congenital anomaly of fetus/newborn); see Section 7.1.11 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

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

7.1.2 SERIOUS ADVERSE EVENTS

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

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

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

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

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.2.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of carcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

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

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

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

expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

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

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The Investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

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

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

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

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

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

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

The following guidance should also be taken into consideration:

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

7.1.9 ABNORMAL LABORATORY VALUE

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

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

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

7.1.10 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 related

to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

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

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

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

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

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

7.3 SAFETY AND TOXICITY MANAGEMENT

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

Safety assessments include the following:

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

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 2000 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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and PI, the DSMB, and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE) or death assessed as related to Study Treatment;
- Three or more subjects experience the same grade 3 or 4 adverse event, assessed as related to Study Treatment;
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to Study Treatment;

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

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

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

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets serious criteria. If the AE is considered serious, the Investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.5 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.6 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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 as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the Investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating Investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.5 and 7.1.6).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability,

reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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.

All complaints must be sent to ClinicalComplaint@inovio.com. Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

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

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

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

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

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a)

recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each arm superior to historical control with a one-sided 0.025 type 1 error level for each hypothesis, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

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

8.5 SUBJECT DISPOSITION

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

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

8.7 MEDICAL HISTORY

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

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are considered those medications taken prior to the first dose of study drug (i.e., Day 0). Concomitant medications are those used on or after Day 0. Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment arm separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

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

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

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated exact Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) vulvoscopy 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 and treatment group as regressor variables.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

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

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

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

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and exact Clopper-Pearson 95% confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

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

8.11.2 LABORATORY DATA

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

8.11.3 VITAL SIGNS

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

8.11.4 PHYSICAL EXAMINATION

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

8.11.5 PATIENT REPORTED OUTCOMES

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

8.11.6 MISSING VALUES

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

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

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

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

Investigator responsibilities relevant to the IRB include the following:

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

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

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

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

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

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

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

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

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

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and for subjects in the imiquimod arm a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

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

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

10.2 SOURCE DOCUMENTS

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

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

10.3 RECORDS RETENTION

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

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

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the Investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 up to four pathologists. Each specimen will be read by two pathologists independently in a masked fashion. The responsibilities and membership structure of the PAC is outlined in the PAC Charter, including the reporting of results.

10.4.3 CLINICAL MONITORING

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.

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

11. PUBLICATION POLICY

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

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CPK	Creatine Phosphokinase
CRF	Case Report Forms
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSMB	Data & Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation with Cellectra™ 2000
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
HSIL	High grade squamous intraepithelial lesion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response Technology
LAST	Lower Anogenital Squamous Terminology
mITT	Modified Intent to Treat
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Participant Diary
PE	Physical exam

PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential
WOMAN-PRO	WOMen with vulvAr Neoplasia PRO

13. REFERENCES

1. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. . Human Papillomavirus and Related Diseases in USA., ICO Information Centre on HPV and Cancer (HPV Information Centre), Summary Report 30 June 2017. 2017.

2. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human Papillomavirus and Related Diseases in Europe. ICO Information Centre on HPV and Cancer (HPV Information Centre) Summary Report 30 June 2017. 2017.

3. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.

4. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.

5. Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjose S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. *Infect Agent Cancer* 2017,**12**:19.

6. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.

7. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.

8. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.

9. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J*, et al.* Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.

10. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.

11. Inovio Pharmaceuticals. Unpublished assessment. 2015.

12. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.

13. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.

14. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.

15. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.

16. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.

17. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

18. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

19. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

20. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

21. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

22. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

23. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

24. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

25. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

26. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

27. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

28. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

29. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

30. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

31. Senn B. Creating and Validating a Patient-Reported Outcome Instrument for Women with Vulvar Neoplasia after Surgical-Treatment - A Mixed-Methods Project, Institute of Nursing Science (INS) University of Basel, University Hospital Berne, Switzerland. 2012.

32. Senn B, Mueller MD, Hasenburg A, Blankenstein T, Kammermann B, Hartmann A*, et al.* Development of a postsurgical patient-reported outcome instrument for women with vulvar neoplasia. *Oncol Nurs Forum* 2012,**39**:E489-498.

33. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) CfBEaRC, Center for Devices and Radiological Health (CDRH). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. 2009.

34. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

35. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

36. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

37. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

38. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA™ 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #13683

Version 3.0
26 March 2019

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] _____

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

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature: _____

_____ _____
Print Name of Principal Investigator Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 2.1 dated 01 December 2017 to Version 3.0 dated 26 March 2019.

1. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. Inovio no longer plans to develop a treatment of VGX-3100 in combination with topical imiquimod. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol and the data will be analysed as planned, but no further participants will be enrolled into this group.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA™ 2000 Alone or in Combination with Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 28 sites in the United States (US) and potentially other countries not yet determined	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3x) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36[3] subjects
Study Duration	100 weeks
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[4] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[5]

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

[4] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

[5] A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL, or vulvar

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[6] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[7] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[8] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

carcinoma at evaluation, or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related treatment for vulvar HSIL.

[6] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

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

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

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of qualifying[9] vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[9] lesion(s) at Week 48, 74 and 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74 and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

[9] A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.
[10] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[9] vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying[9] lesion(s) at Week 74 and/or Week 96 compared to baseline[11]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the efficacy of more than 4 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[12]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit

[11] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.
[12] Additional assessments may include visualization of PD-L1, Granulysin, perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96, and 100.

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

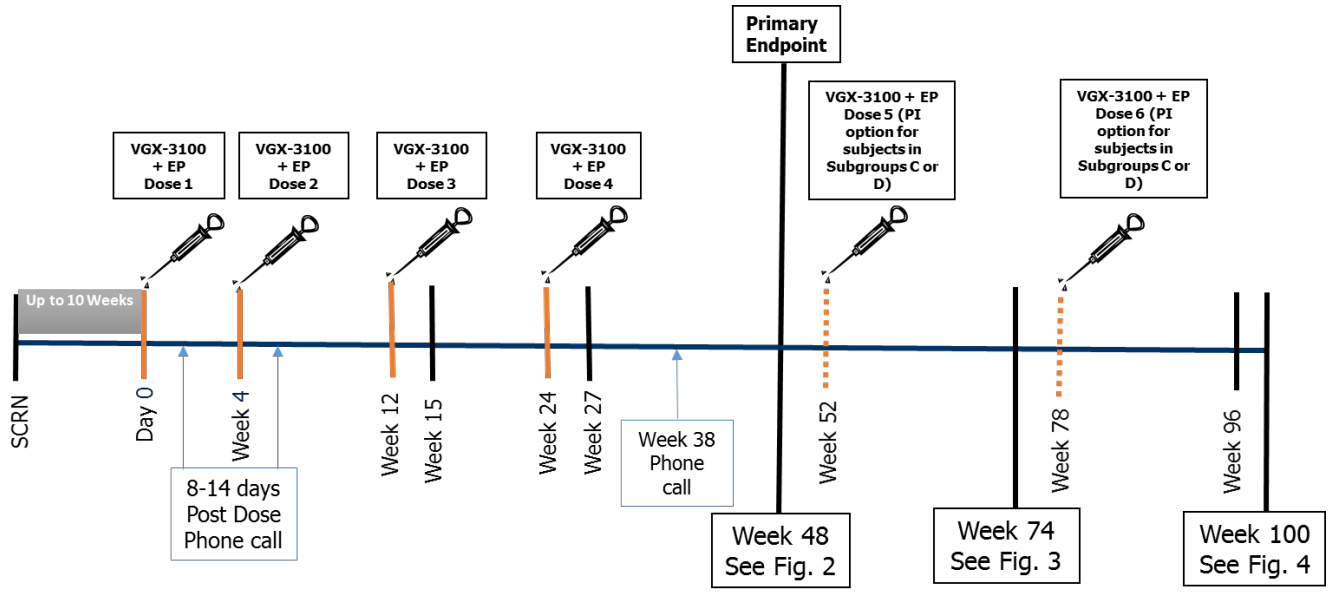
To be eligible for the study, subjects must consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera. Biopsy slides will be sent to the Pathology Adjudication Committee (PAC) by the central laboratory for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen 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 provided and will include the Short Form Health Survey version 2 (SF-36v2™) (Optum), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvAr Neoplasia) Clincial Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

All eligible subjects who consent to participate in the study will receive four to six doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgment of the Investigator. All subjects are scheduled to be followed to Week 100.

Figure 1: Study Visit Schedule



Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod study group will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

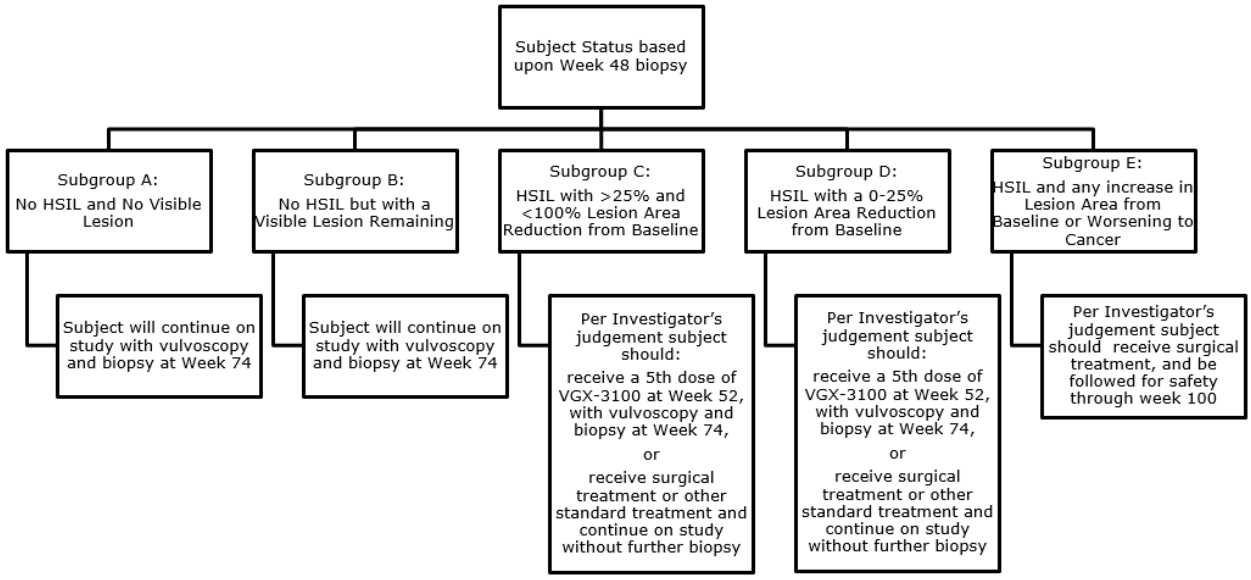
Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0 and Weeks 4, 12, 27, 48, 74 and 96. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same lesion as study start.

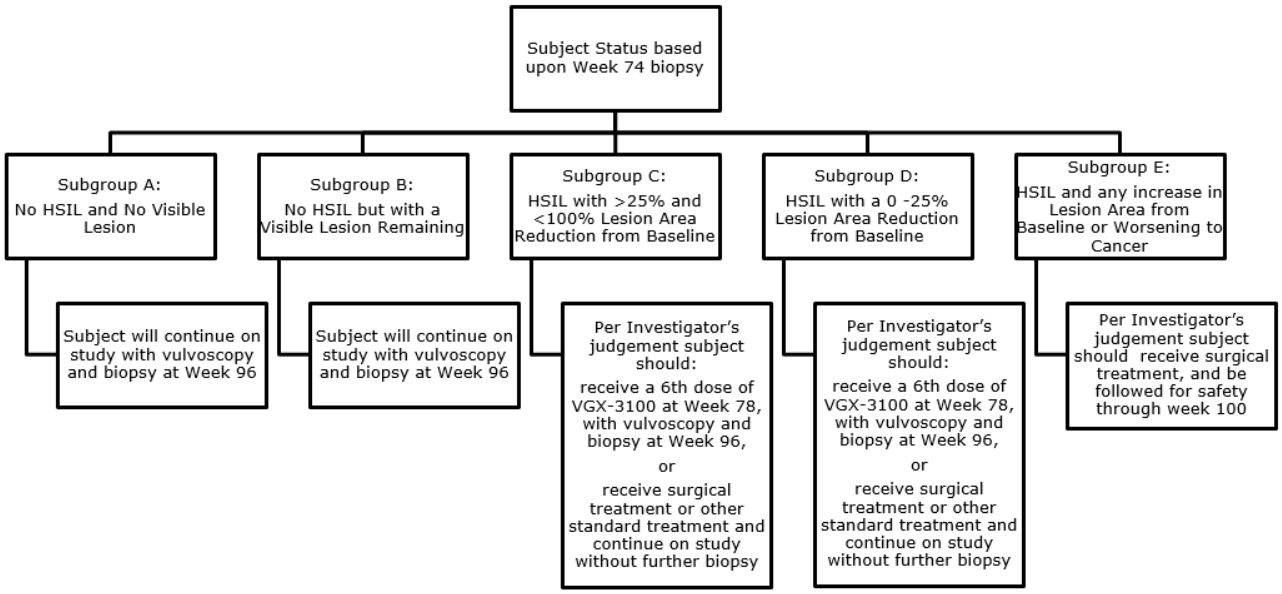
If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy. A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.

Figure 2: Decision process at Week 52



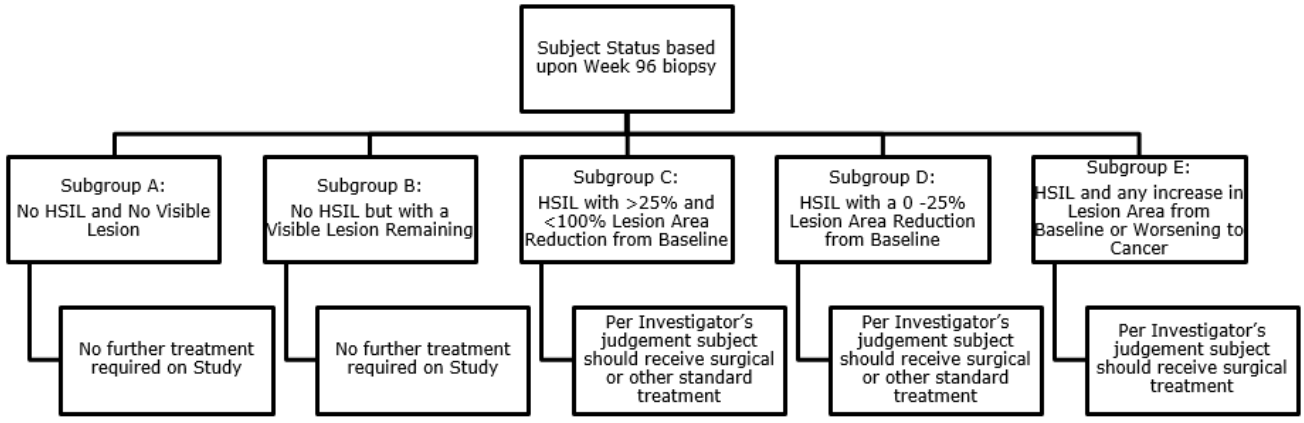
The decision process following results of the Week 74 biopsy are described in Figure 3 and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy of the same area from the region of potentially most advanced disease based upon the judgment of the Investigator. If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

Figure 3: Decision Process at Week 78



The decision process following results of the Week 74 biopsy are as described in Figure 4 and as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

Figure 4: Evaluation process at Week 100



In the event of worsening disease at any time (i.e., Subgroup E – any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. If at any time in the study carcinoma is discovered, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Definition of Responder and Non-responder:Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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

All subjects will be followed for 100 weeks.

Data Safety & Monitoring Board (DSMB): The 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, Principal Investigator (PI) for the trial, and the DSMB.
- If any SAE (or potentially life-threatening AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

Immunogenicity Assessment: The study will explore humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

Virologic Assessment: Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal rinse, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal). At Weeks 48 and 96, cervical sample will also be collected.

HLA haplotyping: A sample from one time point during the study will be tested to explore the relationship between subject HLA haplotypes and regression.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c) Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii) Intrauterine device or intrauterine system;
        iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8) Treatment for genital warts within 4 weeks prior to screening;
9) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream for subjects enrolled prior to Protocol Amendment v3.0 (dated 26Mar2019);
11) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12) 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;
13) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
15) Received any non-study related non-live vaccine within 2 weeks of each study dose;
16) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18) 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

c) 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;
d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
e) 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;
f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
g) Prior major surgery within 4 weeks of Day 0;

19) Participation in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
20) 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 (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);
21) Vulnerable populations:
    a) Active drug 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 service personnel who have the potential to be relocated;
    d) Study-related staff or family members of study-related staff;
22) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	Week 78 (± 14 days)	Week 96 (± 14 days)	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Socio-behavioral assessment	X										X					X
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [a]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[b]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [c]	X															
Pregnancy Testing [d]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[e]	X[e]					X[e]		X[f]		X[e]		X[e]		X[e]	
HLA testing [g]	X															
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Vulvar swabs		X		X		X			X		X		X		X	
Cervical colposcopy		X													X	
Cervical cytology, ThinPrep® [h]		X				X					X				X	
Vulvoscopy [i]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [j]	X	X		X		X			X		X		X		X	
Biopsy [k]	X										X		X		X	
Vulvar HPV genotyping [l]	X										X		X		X	
Inject VGX-3100 +EP [lm]		X		X		X		X				X[m]		X[m]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [n]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [o]			X		X		X		X				X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes (PROs)[p]		X	X	X	X	X	X	X	X		X	X	X		X	X

[a] Full PE mandatory at screening and study discharge (Week 100), 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 BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits.
[c] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 45 days prior to first dose administration.
[d] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.
[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. One additional 8.5 mL yellow (ACD) tube to be collected at Day 0, Week 15 and 48 for microRNA analysis.
[f] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.
[g] HLA testing will performed once from an existing PBMC sample.
[h] HPV genotyping and Pap smears are performed on the same ThinPrep® cervical specimen.
[i] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, and Weeks 74 and 96 for Subgroups C and D unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the PAC for review.
[j] Photography of the acetowhite stained qualifying lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at screening, a post biopsy photo will be sufficient. Additionally, standardized high resolution digital photographic imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.
[k] Tissue specimen from all excised tissue must be reviewed by the PAC and residual vulvar tissue from entry, Week 48, 74 or Week 96 specimen(s) (paraffin blocks or unstained slides) must be sent to the central pathology laboratory for HPV testing.
[l] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.
[m] Potential dosing at Week 52 and Week 78 is applicable for partial responders only.
[n] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.
[o] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.
[p] PRO measures (SF-36v2™, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16/18 is involved in about 83% of HPV-associated vulvar HSIL cases in the U.S. [1] and about 72% in Europe [2]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 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).

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 6,020 new cases and 1,150 attributable deaths annually for year 2017 in the United States [4] and about 9,776 new cases in 2015 in Europe [5]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [6]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 72.1% [4]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [7].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [8].

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which only high grade VIN (2/3) is classified as VIN [9]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [10]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, whichencompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [11]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [12], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [13].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates are as high as 45% at three years post-treatment with all currently available treatment regimens [14, 15].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk

of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [16].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [17]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [16]. Therefore, many patients have a fear of recurrence and progression to cancer [18].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid the use of toilet paper and to rinse with warm water instead. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [19]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [20].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [19]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [20].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [19].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid later development of HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [22]. However, these prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [23].

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan will be used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of subjects in this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study Investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists from the PAC (see Section 10.4.2). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible [24].

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.1). Colposcopy will also be performed at Day 0 and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out suspected disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgment.

1.1.9 VGX-3100

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

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [25, 26]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [27, 28]. 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 [29].

This study will use the CELLECTRA™ 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA™ 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV-16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration study drug is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [30].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Therefore, imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [17].

This study will include a study group to explore whether the efficacy of VGX-3100 is able to be enhanced by concomitant treatment with Imiquimod. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

1.1.15 INCLUSION OF WOMAN-PRO, CLINICAL TRIAL VERSION 2.0

The original WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) was developed by Beate Senn and colleagues [20,31,32] for use following post-surgical intervention. Development of the tool was aligned with the FDA PRO Guidance [33]and included a review of the literature as well as direct patient and expert input. Preliminary measurement properties were assessed in a cross-sectional study. However, despite rigorous development and promising initial measurement properties, gaps in the development and psychometric evaluation exist. To address these gaps, Inovio and collaborators initiated a small qualitative study to confirm the content validity of the tool and support a cross-cultural adaptation of the measure for use in a clinical trial setting of US English and US Spanish speaking subjects. The results of this research is the Clinical Trial of the WOMAN-PRO (2.0) which is utilized in this study.

The WOMAN-PRO Clinical Trial Version 2.0 is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The physical domain is comprised of 15 lesion-related symptoms and includes 5 additional items to measure impact in daily life. Psychosocial constructs are assessment through 11 items that address feelings, thoughts and limitations. Each item is scored using a 4-point Likert scale with higher scores indicating greater difficulty or severity. The recall period is the past week.Details are included in Section 6.8.

1.1.16 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in

duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [34]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.17 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL[6]** on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18[7]** in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of vulvar LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression[8]** of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of the qualifying[9] vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[9] lesion (s) at Week 48, 74 and 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	7a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 7b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits 7c. Flow Cytometry response magnitudes at baseline and Week 27 visits

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[9] vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying[9] lesion (s) at Week 74 and/or Week 96 compared to baseline[11]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the efficacy of 5 or 6 doses of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[12]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Characterize HLA haplotypes and the correlation with efficacy	6. Proportion of subjects with regression of HSIL on histology (i.e. biopsies or excisional treatment) at Week 48 visit
7. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	7. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
8. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	8. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, 96 and 100.

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years).

To be eligible for the study, subjects must sign consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides will be sent to a PAC for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen 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, PRO instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) Clinical Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

The total duration of the study is up to 10 weeks for the screening period and 100 weeks for the treatment and follow-up periods.

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid preferred site, or the anterolateral quadriceps as an alternate site) followed immediately by EP with the CELLECTRA™ 2000 device. As shown in Figure 1, study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. The first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will

receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose at Week 78 per the judgment of the Investigator. Subjects in Subgroup E should receive surgical treatment per the judgment of the Investigator. All subjects will complete the study at Week 100.

Imiquimod treatment – Participants who have been enrolled in the VGX-3100 with imiquimod study group will continue with study visits per protocol, but no further participants will be enrolled into this study group. Subjects randomized to the VGX-3100 with imiquimod study group will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74 and 96. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96 visits. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 4, 12, 27, 48, 74 and 96.

Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same qualifying lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as at study start Investigator(see Table 2). If after

evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy and biopsy of the same lesion as at study start. InvestigatorIf HSIL remains but there is a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy are as described in Figure 4 and are as follows: At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, but from the region of potentially most advanced disease based upon the judgment of the Investigator. (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.

In the event of worsening disease (i.e., Subgroup E - any increase in lesion area from baseline or worsening to cancer), the subject will receive surgical treatment per the Investigator's judgment and will continue on study through Week 100 with vulvoscopy, but without further study treatment or biopsy. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

Table 2: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Acetowhite Lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.
Multiple acetowhite lesions	Vulvar punch biopsies and lesion photography; biopsy should be conducted of the same qualifying lesions as study entry from the region of potentially most advanced disease based upon judgment of the Investigator.

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study

related treatment for vulvar HSIL. Any case of histologically confirmed progression is considered a non-responder. Progression is defined as advancement to carcinoma by histology according to the PAC.

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

Table 3: Definition of Responder and Non-responder

Responder	Non-Responder
Subject with no histologic evidence of vulvar HSIL AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

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

All subjects will be followed for 100 weeks.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data and regression/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, 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 AE) or death assessed as related to study treatment occurs, further enrollment and study treatment will be halted immediately

until a thorough investigation has been conducted by the Medical Monitor, 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 adverse event, assessed as related to study treatment, further enrollment and study treatment will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, 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.

3.4 IMMUNOGENICITY ASSESSMENT

The study will explore humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96.

A blood sample from one time point during the study will be tested to explore the relationship between subject HLA types and regression.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and Vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal only). At week 48 and 96, a cervical sample will also be collected.

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

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

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have confirmed histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;

5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c. Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

4.2 EXCLUSION CRITERIA

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

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;

8. Treatment for genital warts within 4 weeks prior to screening;
9. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream for subjects enrolled prior to Protocol Amendment v3.0 (dated 26Mar2019);
11. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12. 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;
13. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
15. Received any non-study related non-live vaccine within 2 weeks of each study dose;
16. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18. 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
    c) 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;

d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;

e) 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;

f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;

g) Prior major surgery within 4 weeks of Day 0;

19. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);

20. 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 (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);

21. Vulnerable populations:

a) Active drug 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 service personnel who have the potential to be relocated;

d) Study-related staff or family members of study-related staff;

22. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the Investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

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

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document.

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 VIN, 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 she 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 she 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 1). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit (Week 100). A subject will be considered to have completed the study when she completes all scheduled study treatments and follow-up visits.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

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

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study.
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon™) technology. The VGX-3100 formulation to be used in this study is described in Table 4 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently recommended

as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

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

Table 4. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. The actual product label names the product as VGX-3100X; the "X" designation was included to differentiate the current buffer formulation from a previous formulation of VGX-3100 in water. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL]

1 mL/Vial Single Use Vial

Date of Manufacture: _____

Expiry Date: _____

Refrigerate at 2-8°C

CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY

Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: Imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Ophthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours. In the event that Imiquimod is not tolerated at 3 times per week, alternative administration approaches must be discussed and approved by the medical monitor.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

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

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

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

procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor.

5.7 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA™ 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA™ 2000 device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

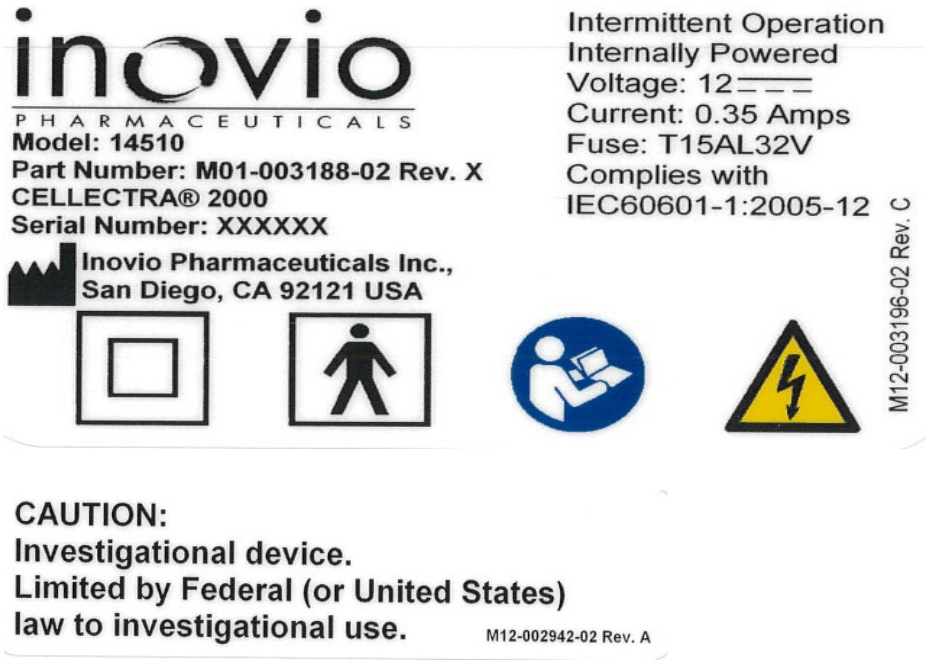
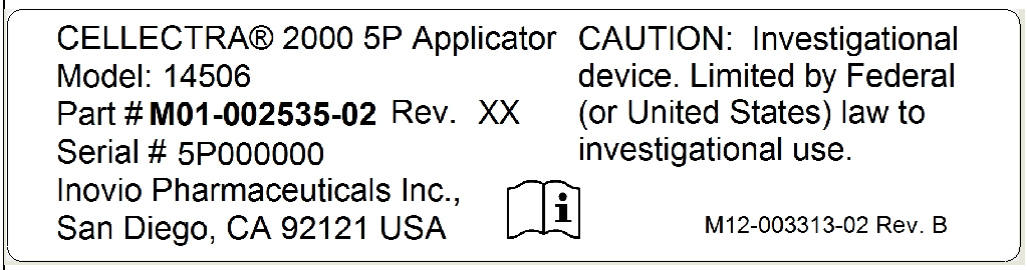
The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 Pulse Generator has a unique serial number, and each CELLECTRA™ 2000 Applicator has a unique serial number. Each CELLECTRA™ 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

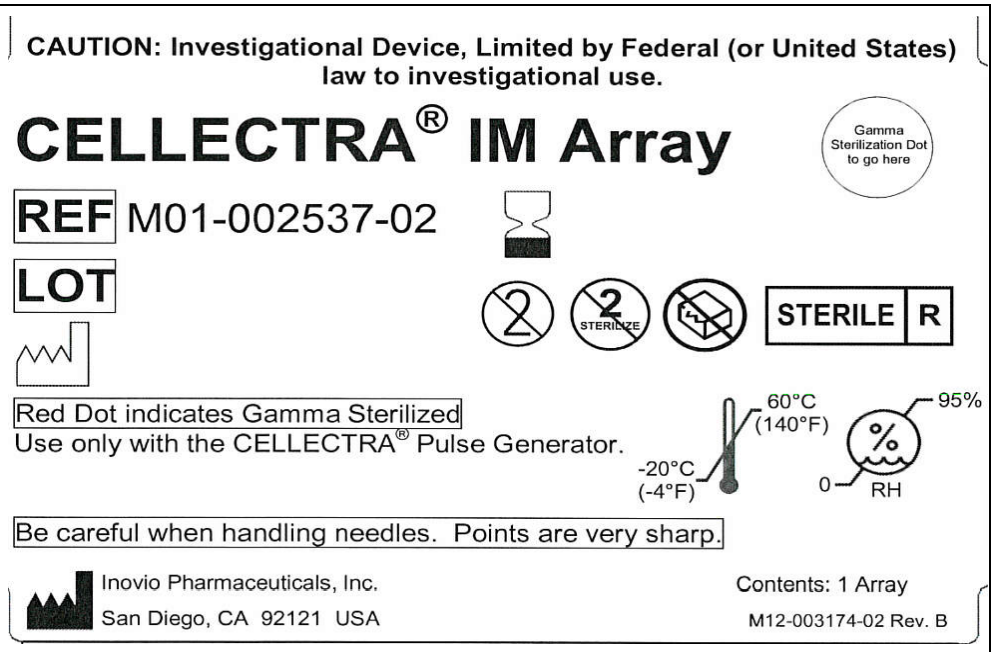
The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 5 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 5. Example Labels for the CELLECTRA™ 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA™ 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA™ 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA™ IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

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

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 2000 serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN OF INVESTIGATIONAL DEVICES

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

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

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted

by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions will not be granted with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct.

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. samples reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

The assessments during the screening period will determine the subjects'' eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments.

The following screening evaluations will be performed within 10 weeks and up to 1 day prior to dosing on Day 0, except for 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.

- Signed informed consent
- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions

- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG **within 45 days prior to Day 0**
- Baseline laboratory evaluations (includes complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed **within 45 days prior to Day 0**
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- HLA typing (may be performed at any time during study; only required to be performed once)
- Vulvoscopy
  - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
  - Photograph of the vulvar lesion(s) must be collected prior to and after biopsy at screening
  - If a **historical biopsy** sample is used to determine eligibility at screening and a pre-biopsy photograph is not available, a post biopsy photo will be sufficient.
- Biopsy:
  - Slides from all excised tissue must be reviewed by the PAC.

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluations will be performed on Day 0 **prior to study treatment**:

- Determination of eligibility per Inclusion/Exclusion Criteria
- Review of concomitant medications and adverse events

- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AE and injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
    - After completing a review of PD 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.

6.2.3 WEEK 4 (± 7 DAYS)

The following study evaluations will be performed at Week 4 **prior to study treatment**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs

- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvar swab
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

The following study evaluations will be performed at Week 4 **after study treatment:**

- Post treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device within 24 – 48 hours of study treatment

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12 (± 7 DAYS)

The following study evaluations will be performed at Week 12 **prior to study treatment:**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Cervical cytology and ThinPrep® for cervical HPV type
  - Collect menstrual cycle status and recent gynecologic history
- Vulvar swab
- Vulvoscopy

- Vulvar lesion photography of the qualifying lesion(s)

The following study evaluations will be performed at Week 12 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device within 24 – 48 hours of study treatment

6.2.6 WEEK 15 (± 7 DAYS)

The following study evaluations will be performed at Week 15:

- Review Adverse Events
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay including miRNA profile

6.2.7 WEEK 24 (± 7 DAYS)

The following study evaluations will be performed at Week 24 **prior to study treatment**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod study group
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device within 24 – 48 hours of study treatment

6.2.8 WEEK 27 (± 7 DAYS)

The following study evaluations will be performed at Week 27:

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48 (± 7 DAYS)

The following study evaluations will be performed at Week 48:

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.11 PATIENT REPORTED OUTCOMESWEEK 52 (± 14 DAYS)

Subjects will have a Week 52 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24 – 48 hours of study treatment

6.2.12 WEEK 74 (± 14 DAYS)

The following study evaluations will be performed at Week 74:

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.13 WEEK 78 (± 14 DAYS)

Subjects will have a Week 78 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Urine pregnancy test (for subjects receiving a 6th dose only)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after study treatment:**

- Post-treatment injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device within 24-48 hours of study treatment

6.2.14 WEEK 96 (± 14 DAYS)

The following study evaluations will be performed at Week 96:

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabsVulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.15 WEEK 100 (± 14 DAYS)

The following study evaluations will be performed at Week 100:

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 RESCREENING OF SCREEN FAILURES

Subjects who sign the informed consent and are assigned a subject identification number (SID) but do not meet the eligibility criteria or fall outside of the screening window will be considered screen failures. If the Investigator believes rescreening is warranted, the Investigator must contact the medical monitor to discuss.

6.3.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique SID, which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.4 SAFETY EVALUATIONS

6.3.4.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge (Week 100). 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. 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.

6.3.4.2 VITAL SIGNS

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.4.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.4.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the Investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.4.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening.

6.3.4.6 LABORATORY EVALUATIONS

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose ≥ 1+) a microscopic examination should be performed.

6.3.4.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.4.8 ELECTROCARDIOGRAM (ECG)

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QT_{cb} or QT_{cf}, ST segment, T wave as well as an Investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as "clinically significant (CS)" or "not clinically significant (NCS)" by the Investigator.

6.3.4.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

The subject will be provided a PD and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell

- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PD will be reviewed with the subject and research staff at 8 -14 Days post-dose.

The study staff will review the PD for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse event accordingly.

6.3.4.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

No serious related adverse events to VGX-3100 have been observed in the clinical trial experience to date. A summary of potential risks of IM Administration followed by EP with CELLECTRA™ can be found in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

Adverse events reported in clinical trials with imiquimod cream, 5% for external genital warts can be found in the imiquimod product label [35], and in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURE

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an

approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to treatment at day 0, Weeks 4 and/or 12. Subjects who receive a mild sedative should not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

Subjects may be offered an analgesic (e.g. acetaminophen, ibuprofen, ketorolac) before or after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, acetaminophen, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.4.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the Investigator will be instructed to use the following grading scale:

Table 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 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. Administration of PRO instruments will be performed according to the validated or otherwise developed procedures and instructions of each respective instrument. The following PRO questionnaires will be used:

1. **WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) Clinical Trial Version – 2.0** (Beate Senn; version modified by Inovio Pharmaceuticals and RTI Health Solutions): is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The recall period is the past week.[20].

   The WOMAN-PRO will be administered on paper only and should be the **first PRO instrument administrated** (i.e. before all other PROs) at each of the following time points:

   - Day 0 (*before* the first study treatment)
   - 8-14 days post dose 1
   - Week 4 (after study treatment)
   - 8-14 days post dose 2
   - Week 12 (after study treatment)
   - Week 15

- Week 24 (after study treatment)
- Week 27
- Week 48 (after biopsy or surgical excision)
- Week 74 (after biopsy or surgical excision)
- Week 96 (after biopsy or surgical excision)
- Week 100

2. **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) [36]. SF-36v2™ will be administered at the following time points:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - 8-14 days post dose 2
    - Week 48 (after biopsy or surgical excision)
    - Week 100
3. **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) [37, 38] and will be administered as described below:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)
    - Week 96 (after biopsy or surgical excision)
    - Week 100
4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered on paper at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74 and 96. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA will occur using plasma obtained at Day 0, Week 15 and 48. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 and 48 samples will be done as a comparison against Day 0, in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun, to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after HPV genotyping and histologic diagnoses have been rendered at Screening, Weeks 48, 74 and 96, then unstained slides and/or the relevant paraffin blocks may be collected for assessment of pro-inflammatory and immunosuppressive elements in tissue, where feasible. Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 HLA TYPING

HLA testing will be performed on PBMC from 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 MHC locus affect the immune response to study treatment. Data arising from this study will be subject to same confidentiality as the rest of the study. This specimen will be destroyed immediately after the analysis and the results checked.

6.12 VULVAR HPV TESTING

At Screening, Weeks 48, 74, and 96, a vulvar punch biopsy sample of approximately 4 mm will be obtained and sent to a central laboratory for HPV genotyping by PCR. In the case of multifocal disease, a vulvar biopsy of approximately 4 mm will be obtained from two lesions that potentially contain the most advanced disease as judged by the Investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching to eliminate potential interference with the results of HPV testing.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of vulvar punch biopsy to eliminate potential interference with the results of HPV testing.

6.13 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Day 0 and at Week 96 for all subjects. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep® test kits at Day 0, Weeks 12, 48 and 96, and read in a central laboratory. HPV PCR will be performed on the ThinPrep® specimen. At each of these visits, menstrual cycle status & recent gynecologic history will be collected. If the Pap smear result suggests progression to cancer the Investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep® samples to eliminate potential interference with the results of HPV testing.

6.14 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74 and 96. Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression. An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected.

Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions that potentially contain the most advanced disease as judged by the Investigator and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74 or Week 96 unless the PI suspects disease progression. All biopsy samples must be sent to the PAC for review. Investigator guidelines for managing the findings of

unscheduled biopsies for suspected disease progression are described in Table 7. Consult the Medical Monitor for any planned departures from these guidelines.

Table 7: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the Investigator suspects disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the Schedule of Events on Table 1. Histologic samples and photographic documentation should be obtained for these cases.

6.15 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given per Investigator discretion and recorded in the appropriate sections of the CRF.

6.16 RESTRICTIONS

The following medications and treatments are prohibited:

- Previous treatment with imiquimod for vulvar HSIL within 4 weeks prior to screening
- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic and ophthalmic corticosteroids are allowed)
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study related live vaccine
- Blood thinners/Anticoagulants within 2 weeks of any study treatment

6.16.1 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the Investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to Investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep® samples.

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal demise, still birth, congenital anomaly of fetus/newborn); see Section 7.1.11 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.2.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of carcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e., there is evidence to suggest a causal relationship between the product and the adverse event). An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (Investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered “unexpected”. Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating Investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating Investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious

expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study Investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The Investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Toxicity Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)
- Death (Grade 5)

The Investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the investigational device. An AE may also be assessed as not related to the IP and/or the investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject’s response to the IP, the Investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The Investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the Investigator as “yes, related” or “no, unrelated” by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the investigational device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event

7.1.9 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the Investigator as clinically significant

7.1.10 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 related

to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject. Subjects who are not withdrawn will continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The Investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 2000 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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and PI, the DSMB, and the IRB/EC (if applicable):

- One third or more subjects experience an AESI assessed as related to Study Treatment;
- Any subject experiences an SAE (or potentially life threatening AE) or death assessed as related to Study Treatment;
- Three or more subjects experience the same grade 3 or 4 adverse event, assessed as related to Study Treatment;
- In the event of two identical, unexpected, Grade 4 toxicities, assessed as related to Study Treatment;

Upon conclusion, the sponsor or designee will notify all Investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

To assure the safety of the subjects, information about all AEs (see Section 7.1), whether volunteered by the subject, discovered by Investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets serious criteria. If the AE is considered serious, the Investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may quality for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.5 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.6 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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 as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the Investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the report will be sent to the Sponsor.

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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating Investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.5 and 7.1.6).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability,

reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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.

All complaints must be sent to ClinicalComplaint@inovio.com. Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, and clearance outside of the vulva, and effect of HLA type on efficacy. Other exploratory analyses pertain to tissue immunological measures and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a)

recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2), and (d) age category (<45 years vs. ≥45 years). There are no requirements for the number of subjects in each stratum. The study is open-label.

The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each study group superior to historical control with a one-sided 0.025 type 1 error level for each hypothesis, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be primary for the analysis of efficacy in this study.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment for all randomized subjects and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the mITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the mITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are considered those medications taken prior to the first dose of study drug (i.e., Day 0). Concomitant medications are those used on or after Day 0. Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment study group separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

The secondary efficacy binary endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

For the analyses, the efficacy time frame is defined by any time starting from 14 days prior to the -specified visit week.

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated exact Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and a) HLA results, b) miRNA results, c) vulvoscopy 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 and treatment group as regressor variables.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

8.11 SAFETY ANALYSES

8.11.1 ADVERSE EVENTS

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and exact Clopper-Pearson 95% confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

Any AEs with a missing or partial onset date will be included in the overall AEs, but not be included within specified day-range summaries. AE duration will be calculated as (Stop Date – Start Date) + 1.

8.11.2 LABORATORY DATA

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values, and categorical response variables will be summarized per time point with percentages, by treatment arm. Baseline is defined as the last measurement prior to the first treatment administration.

8.11.3 VITAL SIGNS

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values

by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

8.11.4 PHYSICAL EXAMINATION

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment study group and by body system, for the mITT population.

8.11.5 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or exact Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.11.6 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

8.11.7 INTERIM ANALYSIS

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

9.2 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE (IRB/EC)

The Investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/EC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/EC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the Investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.

- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The Investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/EC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/EC correspondence with the Investigator must be provided to Sponsor.

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

9.7 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and, for subjects in the imiquimod study group, a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by the Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA)).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

10.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files,

and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

10.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/EC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the Investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 up to four pathologists. Each specimen will be read by two pathologists independently in a masked fashion. The responsibilities and membership structure of the PAC is outlined in the PAC Charter, including the reporting of results.

10.4.3 CLINICAL MONITORING

Clinical Monitoring of the trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
  - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
  - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
  - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOAC).
  - Assure that the study facilities continue to be acceptable
  - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
  - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
  - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

11. PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CPK	Creatine Phosphokinase
CRF	Case Report Forms
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSMB	Data & Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation with Cellectra™ 2000
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
HSIL	High grade squamous intraepithelial lesion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response Technology
LAST	Lower Anogenital Squamous Terminology
mITT	Modified Intent to Treat
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Participant Diary
PE	Physical exam

PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential
WOMAN-PRO	WOMen with vulvAr Neoplasia PRO

13. REFERENCES

1. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. . Human Papillomavirus and Related Diseases in USA., ICO Information Centre on HPV and Cancer (HPV Information Centre), Summary Report 30 June 2017. 2017.

2. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human Papillomavirus and Related Diseases in Europe. ICO Information Centre on HPV and Cancer (HPV Information Centre) Summary Report 30 June 2017. 2017.

3. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.

4. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.

5. Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjose S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. *Infect Agent Cancer* 2017,**12**:19.

6. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.

7. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.

8. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.

9. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J*, et al.* Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.

10. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.

11. Inovio Pharmaceuticals. Unpublished assessment. 2015.

12. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.

13. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.

14. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.

15. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.

16. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.

17. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

18. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

19. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

20. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

21. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

22. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

23. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

24. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

25. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

26. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

27. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

28. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

29. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

30. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

31. Senn B. Creating and Validating a Patient-Reported Outcome Instrument for Women with Vulvar Neoplasia after Surgical-Treatment - A Mixed-Methods Project, Institute of Nursing Science (INS) University of Basel, University Hospital Berne, Switzerland. 2012.

32. Senn B, Mueller MD, Hasenburg A, Blankenstein T, Kammermann B, Hartmann A*, et al.* Development of a postsurgical patient-reported outcome instrument for women with vulvar neoplasia. *Oncol Nurs Forum* 2012,**39**:E489-498.

33. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) CfBEaRC, Center for Devices and Radiological Health (CDRH). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. 2009.

34. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

35. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

36. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

37. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

38. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

HPV-201

A PHASE 2, RANDOMIZED, OPEN LABEL, EFFICACY STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITH CELLECTRA™ 2000 ALONE OR IN COMBINATION WITH IMIQUIMOD, FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE VULVA

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #13683

Version 5.0
19 December 2019

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] M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc.

[redacted]
Date

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals 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 Pharmaceuticals. Any supplemental information added to this document is also confidential and proprietary information of Inovio Pharmaceuticals 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 overseeing the conduct of the trial and approved or given favorable opinion before implementation.

The signature of the Principal Investigator (PI) constitutes the PI's approval of this protocol and provides the necessary assurances that this trial will be conducted in accordance with ICH/GCP and ISO guidelines, local legal and regulatory requirements, and all stipulations of the protocol.

Principal Investigator Signature: _____

_____ _____
Print Name of Principal Investigator Date (DDMMMYYY)

Site Number: _____

Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 3.0 dated 26 March 2019 to Version 5.0 dated 19 December 2019. Protocol Amendment 4.0 was prepared by the Sponsor, but was not distributed to sites nor submitted to the FDA. Since Version 4.0 was finalized internally and never implemented, it was not be incorporated into this protocol. This amendment notes changes since Version 3.0 only. Changes not listed in this summary are administrative and do not affect the safety or subjects, trial scope, or scientific quality of the protocol.

1. Protocol HPV-201 has been amended to end at Week 78 instead of Week 100. This change is prompted by a decision to focus on a 4-dose regimen for the development of VGX-3100 for vulvar HSIL, with the potential for a booster dose at Week 52. A 6th dose will not be pursued, therefore optional dose 6 and the corresponding visits at Weeks 96 and 100 have been removed. Subjects who were already beyond Week 78 or who had received dose 6 prior to Amendment 5.0, will complete the study at the next scheduled timepoint following consent on the associated IRB-approved informed consent form and data collected will be analysed. Cervical colposcopy, scheduled for Week 96, will be done at Week 74 or discharge, for subjects who end the study at Week 78. The socio-behavioral evaluation scheduled for Week 100, will be done at the subjects final discharge visit.
2. The estimated number of Study Centers and Countries/Regions has been updated to more accurately reflect site participation.
3. Secondary endpoint #1b (Protocol Synopsis and Section 2.2) was updated to include adverse events of special interest (AESIs) which is included amongst the adverse events evaluated for secondary objective #1, but was inadvertently not mentioned.
4. Secondary Endpoint #6 was modified to remove Week 74 and 96 from the secondary endpoint analysis since these timepoints are evaluated in Exploratory Endpoint #1.
5. Secondary Endpoints #7a and #7b have been moved to Exploratory Endpoint #8a and #8b.
6. Secondary Endpoint #8 and Exploratory Endpoint #9 have been added to evaluate the efficacy of VGX-3100 treatment alone or in combination with imiquimod, on HPV-16/18 positive vulvar HSIL at Week 48, as HPV-16/18 associated HSIL is considered a significantly higher risk for vulvar cancer.
7. Exploratory Endpoints #2, #3, and #9 have been updated to include the efficacy of four doses as well as more than 4 doses. Clarifying text has been added to Section 8.9 regarding the analysis as it relates to the Week 74 and 96 evaluation according to number of doses received.
8. HLA haplotyping and associated Exploratory Endpoint #6 have been removed from the protocol due to consideration of the results from Inovio's Phase 2 cervical study which showed no clear association of HLA background as a predictor of response. No testing has been performed on HPV-201 subject samples. HLA testing has been removed from all applicable protocol sections and the ICF has been updated to remove this procedure.
9. Section 3.2 and the Protocol Synopsis have been updated to indicate that sites will biopsy all lesions at Weeks 48, 74, and 96 (as applicable). New lesions, and lesions that did not qualify at Screening, should be biopsied post-screening and sent for evaluation. Pathology and genotyping results will be included in the determination of efficacy for the

primary, secondary, and exploratory endpoints. This has been updated accordingly in Section 8.9 of the protocol.

10. Responder and non-responder definitions for the Secondary/Exploratory endpoints have been provided in Section 3.2.
11. The Efficacy Assessment (Protocol Synopsis and Section 3.2) has been updated to differentiate between lesion photographs and lesion measurements. Lesion measurements are only done at Screening, Day 0, Week 48, Week 74, and at Week 96 as applicable.
12. Figure 2 has been updated to align with wording in the protocol indicating that subjects in Subgroup E continue on study with vulvoscopy, but without further study treatment or biopsy, in place of the previous inconsistent wording that subjects in Subgroup E are followed for safety only. All procedures outlined in the schedule of events are conducted on subjects in Subgroup E, except for biopsy or additional study treatment.
13. The Decision process at Week 52 in the Efficacy Assessment (Protocol Synopsis and Section 3.2) has been updated to include new lesions identified at evaluation. A discussion will take place between the Medical Monitor and the Principal Investigator to determine if additional dosing is appropriate when new HPV-16/18 high-grade vulvar lesions are identified.
14. The stopping rules in the protocol synopsis and in Section 7.3.2 have been updated to account for the verification process required following entry of an adverse event into the database.
15. Protocol Administrative Memo #2 (dated 20Dec2017) and #3 (dated 20Aug2018) have been incorporated into the protocol as follows:
    - Exclusion Criteria #15 (in Protocol Version 1.3 dated 21Apr2017, Exclusion criteria #12 in the current protocol) 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 criteria, then the subject should not be excluded on the basis of this criterion.
    - Exclusion Criteria #12 was clarified to indicate that subjects with the presence of any ***unresolved*** abnormal clinical laboratory value greater than Grade 1 per CTCAE v4.03 within 45 days prior to Day 0, or less than **or equal to** Grade 1, but deemed clinically significant by the investigator, will be excluded from the protocol.
    - Section 8.11.2 has been removed as safety labs are done only once at screening, therefore changes in laboratory parameters cannot be analyzed.
16. Section 5.6 has been updated to indicate that authorized site representatives can return unused IP in the absence of the Study Monitor. In addition, as sites adhere to their SOPs for the destruction of unused IP, reconciliation of IP must be provided to the Sponsor or Sponsor designee for review prior to on-site destruction.
17. Section 5.10 has been updated to indicate that an Inovio representative will provide instructions for the destruction and/or return of device materials.
18. Sections 6.2.10, 6.2.12, and 6.2.14 were updated to clarify that lesion photograpy is done pre and post biopsy, and quantitative measurement is done pre-biopsy only
19. The 24 – 48 hour timeframe for download of EP data from the device was removed from Sections 6.2.1, 6.2.3, 6.2.5, 6.2.7, 6.2.11, and 6.2.13. It is essential that data is

downloaded, however the requirement to complete this task within 24 – 48 hours of electroporation was unnecessarily restrictive.

20. The timeframe around daily activity for grading injection site reactions has been defined in Table 11. The Sponsor defined timeframe for daily activity, is an impact lasting ≥ 24 hours.
21. Changes in safety lab parameters as an assessment performed by the Medical Monitor has been removed from Section 7.3 since safety labs are done only once at screening. Adverse events that arise as a consequence of lab abnormalities will be recorded as AEs per section 7.1.9 and will be assessed by the Medical Monitor.
22. The Medical Monitor for this study has changed. The contact information for the Medical Monitor has been updated on the Medical Monitor Approval Page and in Section 7.4.2.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: A Phase 2, Randomized, Open Label, Efficacy Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with CELLECTRA™ 2000 Alone or in Combination with Imiquimod, for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Vulva	
Estimated Number of Study Centers and Countries/Regions: Approximately 20 sites in the United States (US)	
Study Phase: 2	
Hypothesis: Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 given alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL[1] associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.	
Dose of VGX-3100	6 mg (1 mL)
Dose of Imiquimod	12.5 mg imiquimod 5% topical cream
Administration	Intramuscular injection followed by EP with the CELLECTRA™ 2000 device alone or in combination with topical imiquimod
VGX-3100 Dosing Schedule	Day 0, Weeks 4, 12, and 24, with additional doses given to partial responders at Weeks 52 and 78
Imiquimod Dosing Schedule	Three times per week (3x) from Day 0 through Week 20[2]
No. of Subjects	Approximately 36[3] subjects
Study Duration	Up to 100 weeks[4]
Primary Objective	Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue
Primary Endpoint	Proportion of subjects with no histologic evidence of vulvar HSIL[5] and no evidence of HPV-16/18 at Week 48 in vulvar

[1] Throughout this protocol high grade disease (previously known as VIN2 or VIN3) is referred to as vulvar HSIL according to the 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions and 2012 consensus recommendation on Lower Anogenital Squamous Terminology (LAST) from the American Society of Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists (CAP).

[2] Inclusive of administration on day of dosing.

[3] The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

[4] Protocol amendment 5.0 removes Week 96 and 100 from the schedule of events as well as optional dose 6 at Week 78. Data collected on subjects who have already completed these visits and received dose 6 at the time of IRB approval, will be analysed as planned

[5] No evidence of vulvar HSIL is defined as normal tissue or vulvar LSIL (VIN 1) or condyloma

	tissue samples (i.e. collected via biopsy or excisional treatment)[6]
Secondary Objectives	**Associated Secondary Endpoints**
1. Evaluate **the safety and tolerability** of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, AESIs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)[4]
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL**[5] on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18**[7] in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression**[8] of vulvar HSIL to vulvar cancer from baseline to Week 48 visit

[6] A treatment responder for the primary endpoint is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is defined as a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 in vulvar tissue at evaluation, or a subject who received non-study related treatment for vulvar HSIL.
[7] Clearance of HPV-16 or HPV-18 is defined as being undetectable by PCR assay.
[8] Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.

6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of qualifying[9] vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Week 48 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
7. Describe the **cellular immune response** to VGX-3100, administered alone or in combination with imiquimod, post dose 4	7. Flow Cytometry response magnitudes at baseline and Week 27 visits
8. Determine the efficacy of four doses of VGX-3100 alone or in combination with imiquimod with respect to histopathologic regression of vulvar HSIL or virologic clearance of HPV-16/18 in vulvar tissue	8. Proportion of subjects with no histologic evidence of vulvar HSIL[5] or no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)

[9] A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.
[10] Baseline photographic imaging is defined as photographs obtained at Day 0 prior to the first study dose. Digital photos will be analyzed with a computer program to calculate the total lesion size in cm^2.

Exploratory Objectives	Associated Exploratory Endpoints
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[9] vulvar lesion(s), in subjects who did not have complete lesion resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of qualifying lesion(s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction) and complete lesion resolution (no visible lesion).
2. Describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSIL on histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100
3. Describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	6. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
7. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	7. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, and Weeks 96, and 100 as applicable.

[11] Additional assessments may include visualization of PD-L1, Granulysin, perforin, CD137, CD103 and possibly other relevant markers identified in the literature in vulvar tissue as sample allows.

8. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 8b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits
9. Determine the long term efficacy of VGX-3100 alone or in combination with imiquimod with respect to histopathologic regression of vulvar HSIL or virologic clearance of HPV-16/18 in vulvar tissue	9. Proportion of subjects with no histologic evidence of vulvar HSIL[5] or no evidence of HPV-16/18 at Week 74 and 96 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)

Study Design:

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or 18. Approximately 36 subjects will be enrolled. Approximately twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2) on Day 0, and (d) age category (<45 years vs. ≥45 years) on Day 0.

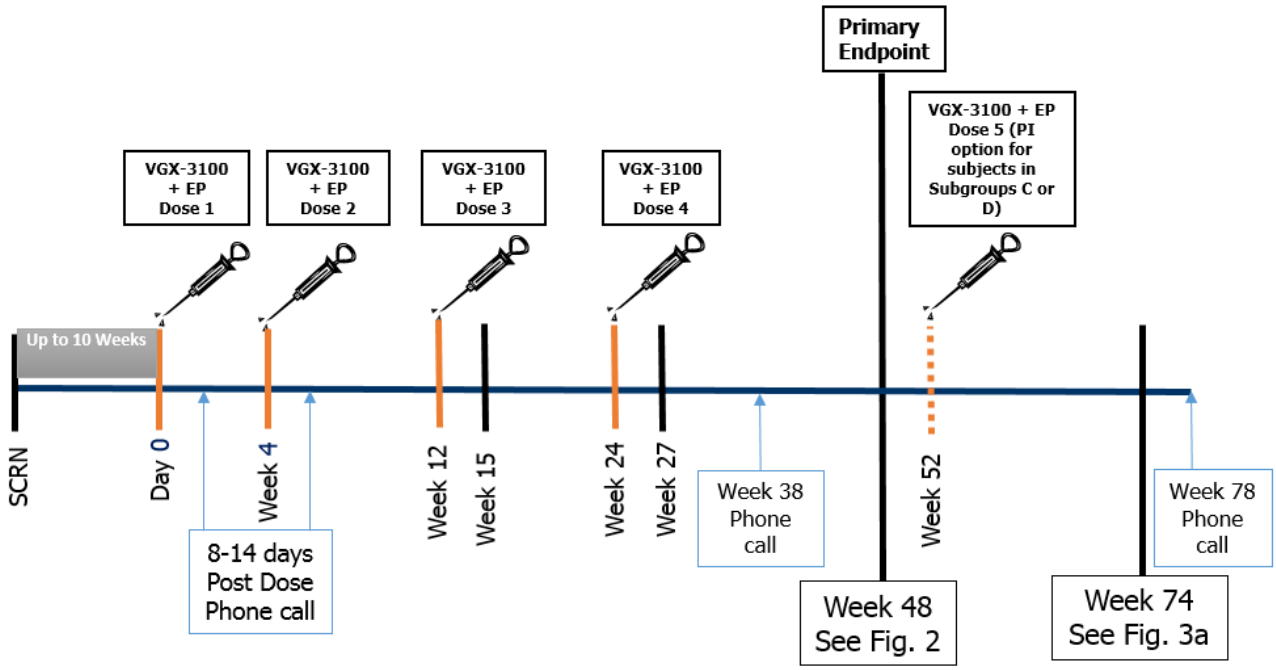
To be eligible for the study, subjects must consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera. Biopsy slides will be sent to the Pathology Adjudication Committee (PAC) by the central laboratory for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar tissue specimen 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 provided and will include the Short Form Health Survey version 2 (SF-36v2™) (Optum), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvAr Neoplasia) Clincial Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

All eligible subjects who consent to participate in the study will receive at least four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria, but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM followed immediately by EP with the CELLECTRA™ 2000 device. Figure 1 (Appendix A) shows the original study visit schedule in which study subjects receive 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. Figure 1a below shows the revised visit schedule per Protocol Amendment 5.0. In both schedules, the first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator.

Figure 1a: Revised Study Visit Schedule, Protocol Amendment 5.0



With Amendment 5.0, subjects will complete the study at Week 78 and will not be offered a 6th dose. Subjects who were beyond Week 78 at the time of IRB approval of Amendment 5.0, will return for their final visit at their next scheduled timepoint as outlined in Table 1. Subjects must sign the IRB-approved informed consent document for Amendment 5.0 prior to the initiation of procedures for their final study visit.

Imiquimod treatment - Subjects randomized to the VGX-3100 with imiquimod study group will apply imiquimod 5% cream to the vulvar lesion(s) beginning in the evening on Day 0, and will continue to apply imiquimod cream three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

Efficacy Assessment: Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in length. Visible lesion must remain after screening biopsy to ensure measurement on study.

Visualization of a normal appearing vulva by vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and at Week 96 for subjects reaching Week 96 prior to Amendment 5.0 or for whom this is the final visit. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed and photographed during vulvoscopy at Screening, Day 0 and Weeks 4, 12, 27, 48, 74, and at Week 96 for subjects who have reached this timepoint prior to Amendment 5.0 or for whom this is the final visit. Using standardized high resolution digital

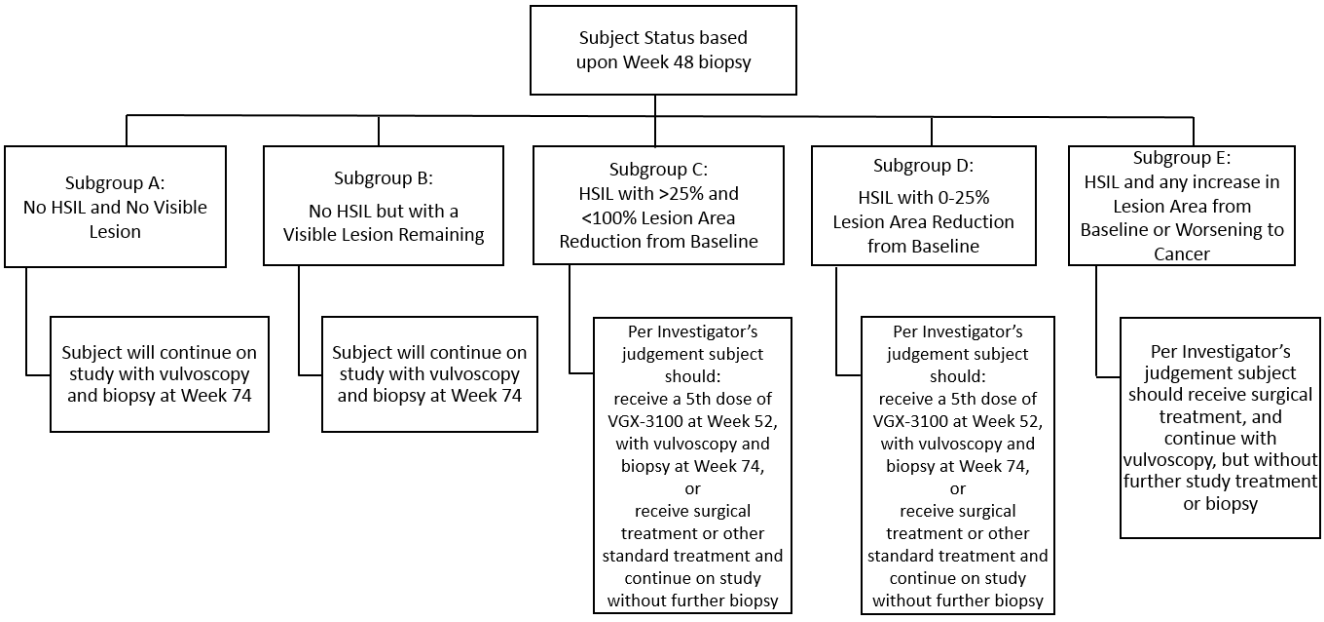
photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, Weeks 48, 74, and at Week 96 for subjects who have reached that timepoint prior to Amendment 5.0 or for whom this is their final visit.

The decision process following results of the Week 48 biopsy are described in Figure 2 below and as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start, from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures).

If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same lesion(s) as study start.

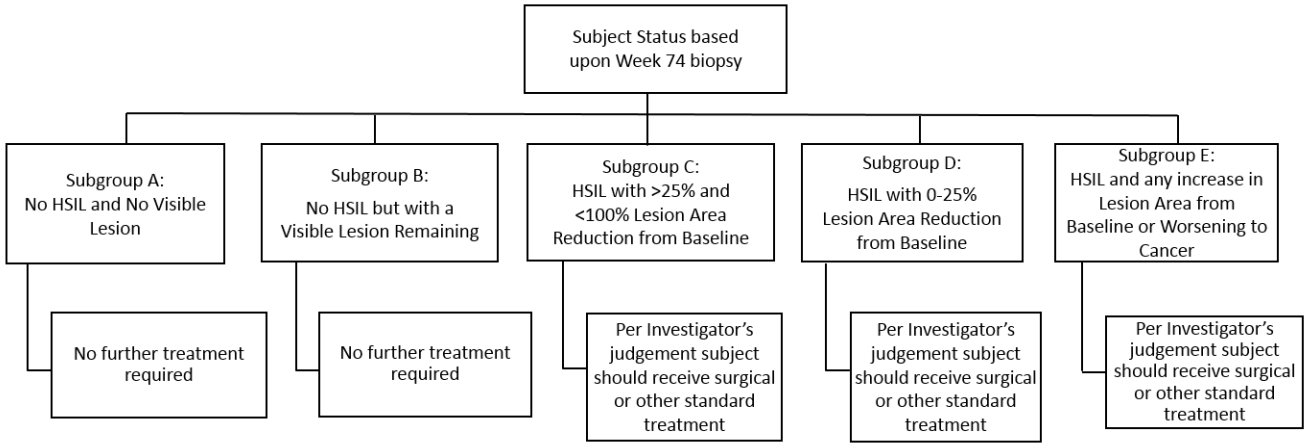
If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy. A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.

Figure 2: Decision process at Week 52



The decision process following results of the Week 74 biopsy for subjects who completed this visit prior to Amendment 5.0 are described in Figure 3 (Appendix B) for the original study design. The evaluation process following results of the Week 74 biopsy under Amendment 5.0 are described in Figure 3a below and as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2).

Figure 3a: Evaluation Process at Week 78, Amendment 5.0



If, after evaluation of Week 74 biopsy tissue by the PAC, there is no evidence of HSIL (Subgroups A or B), the Investigator will use their clinical judgment regarding follow-up care of the subject (not part of study activities).

If, after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the subject will receive further standard of care treatment (not part of study activities) per the Investigator's judgment.

The decision process for subjects who are beyond Week 78 at the time of IRB approval of Amendment 5.0 can be found in Appendix C. These subjects will complete the study at their next scheduled visit as outlined in Table 1. Subjects must sign the IRB-approved informed consent document for Amendment 5.0 prior to the initiation of procedures for their final study visit.In the event of worsening disease prior to the end of the study (i.e., Subgroup E), the subject will receive surgical treatment per the Investigator's judgment and will continue on study with vulvoscopy, but without further study treatment or biopsy. In the event of worsening disease at the final visit, the subject will receive standard of care treatment (not part of study activities) per their treating physician. If wide excision is conducted at or prior to the subjects last on site visit, the sample obtained will be sent to the PAC for evaluation.

If at any time in the study carcinoma is discovered, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4. If wide excision is required, the sample obtained will be sent to the PAC for evaluation.

All visible lesions should be biopsied at Week 48. For subjects whom Week 78 is their final visit, all visible lesions should be biopsied at Week 74. For subjects whom the final visit is Week 96, all visible lesions should be biopsied at Week 96.

If there is a new lesion identified at evaluation, or a non-qualifying lesion is rebiopsied and confirmed on study to be vulvar HSIL and HPV-16/18 positive at evaluation, a discussion will take place between the Medical Monitor and the Principal Investigator to determine if additional dosing is appropriate.

Definition of Responder and Non-responder for the Primary Endpoint: Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL. A treatment responder is defined as a subject with no histologic evidence

of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression from HSIL to carcinoma is considered a non-responder.

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
2) All adverse events including SAEs, AESIs, SUSARs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed through Week 78 under Amendment 5.0, or up to 100 weeks if beyond week 78 at the time of Amendment 5.0.

Data Safety & Monitoring Board (DSMB): The 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) 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 (PI) 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, 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 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, PI 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, 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.

Immunogenicity Assessment: The study explores humoral and cell mediated immune responses to VGX-3100, and VGX-3100 with imiquimod, in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96. Samples will not be obtained at Week 96 for subjects who complete the study prior to this timepoint, per Amendment 5.0.

Virologic Assessment: Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal rinse, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal). Samples will

not be obtained at Week 96 for subjects who complete the study prior to this timepoint, per Amendment 5.0. At Weeks 48 and 96, a cervical sample will also be collected.

Study Population:

Inclusion:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;
5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
   a) Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
   b) Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
   c) Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
      i) Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
      ii) Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
      iii) Intrauterine device or intrauterine system;
      iv) Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Has normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

Exclusion:

1) Untreated microinvasive or invasive cancer;
2) Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3) Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4) Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5) Biopsy-proven differentiated VIN;
6) Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7) Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;
8) Treatment for genital warts within 4 weeks prior to screening;
9) Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10) Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream for subjects enrolled prior to Protocol Amendment v3.0 (dated 26Mar2019);
11) Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12) Presence of any unresolved abnormal clinical laboratory values greater than Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 within 45 days prior to Day 0 **or** less than or equal to Grade 1 but deemed clinically significant by the Investigator;
13) Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14) History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®9, Gardasil®, Cervarix®);
15) Received any non-study related non-live vaccine within 2 weeks of each study dose;
16) Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17) Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18) 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;

c) 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;
d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;
e) 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;
f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;
g) Prior major surgery within 4 weeks of Day 0;

19) Participation in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);
20) 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 (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);
21) Vulnerable populations:
a) Active drug 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 service personnel who have the potential to be relocated;
d) Study-related staff or family members of study-related staff;
22) 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.

STUDY SCHEDULE OF EVENTS

Table 1: Schedule of Events

Tests	Screen (-10 wk to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 7 days)	8-14 days post dose 2 Phone Call	Week 12 (± 7 days)	Week 15 (± 7 days)	Week 24 (± 7 days)	Week 27 (± 7 days)	Week 38 (± 7 days) Phone Call	Week 48 (± 7 days)	Week 52 (± 14 days)	Week 74 (±14 days)	*Week 78 (± 14 days) Phone Call	Week 96 (± 14 days)	Week 100 (± 14 days)
Informed consent	X															
Medical History/Demographics	X															
Medications (prior/concomitant)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Socio-behavioral assessment [a]	X										X					X[a]
Inclusion/Exclusion criteria	X	X														
Randomization		X														
Physical exam (PE)/assessment [b]	X	X		X		X		X	X		X	X	X	X[b]	X	X
Vital signs	X[c]	X		X		X		X	X		X	X	X	X[c]	X	X
Screening safety (12 lead ECG, labs) [d]	X															
Pregnancy Testing [e]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[f]	X[f]					X[f]		X[g]		X[f]		X[f]		X[f]	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Vulvar swabs		X		X		X			X		X		X		X	
Cervical colposcopy [h]		X											X[h]		X[h]	
Cervical cytology, ThinPrep® [i]		X				X					X				X	
Vulvoscopy [j]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [k]	X	X		X		X			X		X		X		X	
Biopsy [l]	X										X		X		X	
Vulvar HPV genotyping [m]	X										X		X		X	
Inject VGX-3100 +EP [n]		X		X		X		X				X[n]		X[n]		
Post treatment reaction assessment		X		X		X		X				X[n]		X[n]		
Dispense imiquimod + distribute imiquimod dosing log [o]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X[n]		X[n]		
Review PD [p]			X		X		X		X				X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes (PROs)[q]		X	X	X	X	X	X	X	X		X	X	X		X	X

*Under Protocol Amendment 5.0, subjects will complete the study at Week 78, which may be completed by phone. Subjects who are beyond Week 78 at the time of IRB approval of the amendment, will complete the study at their next scheduled visit.

[a] Subjects completing the study before Week 100 per Amendment 5.0, will have the final socio-behavioral assessment done at their final discharge visit. This may be obtained by phone.

[b] Full PE mandatory at screening and study discharge (Week 100 for subjects completing this visit before Amendment 5.0), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE. PE will not be conducted on subjects completing the study with a Week 78 phone call, per Amendment 5.0.

[c] Screening vital signs must include a measured height and weight and calculated BMI (Bodyweight in kilograms divided by height in meters squared). Weight will be measured at all dosing visits. Vital signs will not be collected on subjects completing the study with a Week 78 phone call, per Amendment 5.0.

[d] Screening 12-lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, CPK and urinalysis performed within 45 days prior to first dose administration.

[e] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.

[f] 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. One additional 8.5 mL yellow (ACD) tube to be collected at Day 0, Week 15 and 48 for microRNA analysis.

[g] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.

[h] Cervical colposcopy will be performed once at Day 0, and once at Week 96. For subjects completing the study at Week 78, the repeat cervical colposcopy will be performed at Week 74 or the discharge visit.

[i] HPV genotyping and Pap smears are performed on the same ThinPrep® cervical specimen.

[j] An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening), Week 48, Week 74, and Week 96 for subjects in Subgroups C and D prior to Amendment 5.0, unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples obtained prior to or at the subjects final discharge visit (if not a phone visit) must be sent to the PAC for review.

[k] Photography of the acetowhite stained qualifying lesion(s) must be performed prior to and after biopsy, and at all vulvoscopy examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at screening, a post biopsy photo will be sufficient. Additionally, standardized high resolution digital photographic imaging should be obtained during examinations of the vagina if lesions are identified, for documentation.

[l] Tissue specimen from all excised tissue obtained prior to or at the subjects in-person discharge visit must be reviewed by the PAC and will be sent to the central laboratory for HPV testing. All lesions will be biopsied at Week 48, 74, and 96 (as applicable), per Amendment 5.0.

[m] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.

[n] Potential dosing, post-treatment assessment, and distribution of the Participant Diary at Week 52 and Week 78 is applicable for partial responders only. Partial responders who reach Week 78 after Amendment 5.0 will not be offered a 6th dose.

[o] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.

[p] A phone call will be used to review the Participant Diary (PD) with subject within 8-14 days following dose 1 and 2. The patient will be expected to bring the PD to the next visit for review.

[q] PRO measures (SF-36v2™, EQ-5D-5L, WOMAN-PRO) plus two additional questions will be assessed as described in Section 6.8.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 HUMAN PAPILLOMAVIRUS AND INFECTION

Human papillomaviruses (HPV) are double-stranded DNA viruses with more than 100 genotypes some of which can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) causing generally benign lesions. HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [1].

HPV-16/18 is involved in about 83% of HPV-associated vulvar HSIL cases in the U.S. [1] and about 72% in Europe [2]. Persistent infection with one or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic high grade squamous intraepithelial lesions (HSIL).

HPV causes more cancers than any other virus. In U.S. archival tissues of cancers diagnosed from 1993 to 2005, HPV DNA was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 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).

1.1.2 VULVAR CANCER

Vulvar HSIL can lead to vulvar cancer with an estimated 6,020 new cases and 1,150 attributable deaths annually for year 2017 in the United States [4] and about 9,776 new cases in 2015 in Europe [5]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [6]. Differentiated VIN, which is typically not caused by HPV infection and is more typically found in older women, is more likely to progress to cancer more rapidly than HPV-associated-VIN. The five year overall relative survival for vulvar cancer in the U.S. is 72.1% [4]. Recurrent vulvar cancer occurs in an average of 24% of cases after primary treatment, after surgery with or without radiation [7].

1.1.3 VULVAR INTRAEPITHELIAL NEOPLASIA (VULVAR HSIL)

HPV-associated vulvar intraepithelial neoplasia (VIN) is a chronic (typically persisting for years), premalignant disorder of the vulvar skin that is caused by persistent infection with one or more high-risk genotypes of HPV. Infected cells produce E6 and E7 oncoproteins constitutively, which increases the degradation of cell cycle regulation proteins p53 and pRb, respectively, resulting in unrestricted cell growth and neoplasia. The basis for progression to cancer is, therefore, attributed to the viral proteins E6 and E7. VGX-3100 specifically induces immune responses against E6 and E7, thereby enabling clearance of pre-malignant cells as demonstrated in the Phase 2 study of cervical HSIL [8].

In 2004, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the three grade classification system with the current single grade classification for which only high grade VIN (2/3) is classified as VIN [9]. In 2012, the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated lesions applied the term high grade squamous intraepithelial lesion (HSIL) to encompass high grade dysplasia [10]. Therefore, for the purpose of this study, the term vulvar HSIL will be used, whichencompasses VIN 2 and VIN 3; the term 'vulvar LSIL' will be used to encompass what was previously known as VIN 1.

Once vulvar HSIL has developed, spontaneous regression is rare, likely occurring in only 1.5% to 5% of women [11]. Over time, typically years, vulvar HSIL can progress to invasive cancer of the vulva, e.g. from treated patients, median: 2.4 years in one group and median 13.8 years in another group [12], and from VIN3 patients, mean = 2.5 years, range: 4 – 216 months [13].

Vulvar HSIL remains a significantly undermet medical condition for the following reasons which will be described further: 1) the rate of recurrence of vulvar HSIL under currently used surgical and medical approaches is extremely high, 2) there is a high psychological and physical negative impact of surgery, 3) vulvar HSIL is symptomatic and impacts activities of daily living, 4) prophylactic HPV vaccines have no therapeutic activity against vulvar HSIL and have not achieved universal uptake, leaving a population of susceptible and impacted women, and 5) the early diagnosis of vulvar HSIL is limited to visual inspection with biopsy.

1.1.4 RECURRENT DISEASE WITH CURRENT THERAPEUTIC OPTIONS

There remains an unmet medical need with regard to effective treatment options for vulvar HSIL. Current treatment options show a significant risk of vulvar HSIL recurrence, often requiring multiple, repeat treatments. Progression to vulvar cancer following current vulvar HSIL treatments can also occur within 1 year of treatment and for up to 20 years post treatment. The current treatment options for vulvar HSIL are surgical excision, laser ablation, and off-label medical therapy. The rate of HPV-associated vulvar HSIL recurrence after surgical treatment is high; post-treatment recurrence rates are as high as 45% at three years post-treatment with all currently available treatment regimens [14, 15].

Wide local excision is the 'preferred initial intervention' by ACOG if invasive carcinoma is suspected, and, vulvar biopsy shows vulvar HSIL. If occult invasive disease is not suspected, vulvar HSIL treatment includes surgery: wide local excision, partial vulvectomy, skinning vulvectomy, or simple vulvectomy, laser ablation. Surgical treatments are associated with disruption of normal anatomy and subsequent issues with body image and sexual dysfunction. Medical therapies have been investigated as a means to avoid these negative outcomes. Clinical trials have shown the application of topical imiquimod to be effective however it has not been approved by the U.S. Food and Drug Administration for this indication. Inconsistent treatment efficacy results have been shown with photodynamic therapy, topical cidofovir and topical 5-flourouracil.

Vulvar HSIL may be followed (with interim observation, but, no intervention) if the patient is young, and, or, if the immune-compromised state is being corrected. Women with pathologic clear margins (no vulvar HSIL) after surgical excision have a lower, yet significant, risk of recurrence compared to women with involved margins. Laser ablation is acceptable treatment for vulvar HSIL when cancer is not suspected, although the risk

of recurrence is slightly higher compared to wide local excision. Laser treatment of vulvar HSIL requires destruction of cells through the entire thickness of the epithelium including hair follicles (in hair-bearing areas of the vulva). In areas without hair, ablation should extend through the dermis. Post-treatment recurrence rates exceed 30% (for all treatment regimens), and is higher with positive excision margins [16].

1.1.5 PSYCHOLOGICAL AND PHYSICAL IMPACTS OF CURRENT THERAPEUTIC OPTIONS

Virtually all patients with HPV-related Vulvar HSIL will require treatment, given the low rate of spontaneous resolution. According to the current ACOG & ASCCP guideline for management of VIN, because of the potential for occult invasion and if cancer is suspected (even if biopsy shows vulvar HSIL), the standard treatment of vulvar HSIL is wide local excision (i.e. surgery) [17]. When occult invasion is not a concern, vulvar HSIL can be treated with excision, laser ablation, or topical imiquimod as an off-label medical therapy.

Current treatment options are associated with pain, disfigurement and a recurrence rate as high as 45% at three years post-treatment [16]. Therefore, many patients have a fear of recurrence and progression to cancer [18].

In excisional treatment, patients are advised to rest for two weeks, including delaying return to work for up to one week, and to avoid sexual intercourse for up to 5 weeks. Furthermore, patients are instructed to avoid baths and exercise for a few weeks, and some women are advised to avoid the use of toilet paper and to rinse with warm water instead. During recovery, common effects include pain in urinating and wiping, soreness, difficulty sitting, and feeling tired [19]. In the first week after hospital discharge, common patient-reported symptoms and other effects include swelling, drainage, pain, bleeding, numbness, redness, hardness, burning, pressure, unusual odor, changed skin color, opening of suture, warmth, itching, scarred skin, tiredness (including some feeling of exhaustion), insecurity, feeling of changed body, sexual concerns, anxiety, sadness, changed feeling in self-confidence, and difficulties in partnership [20].

1.1.6 IMPACT OF VULVAR HSIL UPON ACTIVITIES OF DAILY LIVING

The presence of vulvar HSIL is frightening and can have long-lasting effects on well-being [19]. The symptoms and signs of vulvar HSIL can be moderate to severe and include painful sexual intercourse, itching or burning, and visible lesions.

In the first week after hospital discharge from surgical excision, common patient-reported impacts on daily life include difficulties sitting, wearing clothes (e.g. underwear, pants), carrying out activities (e.g. climbing stairs, cooking), bowel movements, and urinating [20].

In a study of sexual function and quality of life after excisional treatment, vulvar HSIL patients reported significantly poorer scores in sexual function and quality of life than age-matched healthy women. During the post-treatment follow-up phase of about one year, until given assurance of lesion clearance some patients report the sense that they are in the doctor's office all the time [19].

1.1.7 LIMITATIONS OF PROPHYLACTIC HPV VACCINES

Immunization with prophylactic vaccines represents the initial recommended approach within the pediatric and young female populations to avoid later development of HPV-associated vulvar HSIL and subsequent vulvar cancer. The US-licensed prophylactic HPV vaccines are indicated for girls and women ages 9 through 26 years for Gardasil® and Gardasil®9 (Merck & Co. Inc.), and ages 9 through 25 years for Cervarix® (GlaxoSmithKline). The early portions of these age ranges are generally before sexual debut and thus can allow immunologic protection against the anticipated earliest normal exposures to HPV infection. HPV prophylactic vaccination is highly effective and safe, and routine vaccination is recommended for females in the United States starting at age 11 or 12 years [22]. However, these prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [23].

1.1.8 ENHANCED MONITORING PLAN

An enhanced monitoring plan will be used in this study to address the risk of a potential delay in treatment of vulvar HSIL. The feasibility of this approach was demonstrated in the Phase 2b study of cervical HSIL. Given that vulvar disease progresses slowly to vulvar cancer if untreated, the proposed enhanced monitoring plan is expected to maintain the safety of subjects in this study. First, only Gynecology-Oncologists and Gynecologists who are well experienced in the monitoring and management of vulvar disease will be used as study Investigators. Inclusion into the study will require histologic confirmation of the diagnosis of the vulvar disease as vulvar HSIL, and not carcinoma, by two independent expert pathologists from the PAC (see Section 10.4.2). Women with differentiated VIN, which is more likely to progress faster and is not typically HPV-related is specifically excluded from study entry. By contrast, HPV-associated vulvar HSIL does not progress rapidly, typically taking years to manifest and progress, making enhanced monitoring feasible [24].

Throughout the study, there will be frequent vulvoscopy as well as photographic documentation and analysis of the lesion size (see Section 6.1). Colposcopy will also be performed at Day 0 and during the study given that concurrent disease in the lower genital tract can occur. A Data Safety Monitoring Board will be utilized to review subject safety data and advise on any study-level safety concerns. Investigators always have the option of performing ad hoc vulvar biopsies to rule out suspected disease progression. Additional treatment (e.g., additional excision, ablation, or medical therapy) may be carried out, if deemed necessary according to Investigator judgment.

1.1.9 VGX-3100

VGX-3100 encodes HPV-16 E6/E7 and HPV-18 E6/E7 antigens. The plasmids were designed and constructed using proprietary synthetic vaccine (SynCon™) technology. This process involves synthetically deriving consensus genes across multiple strains and optimizing DNA inserts at the genetic level to allow high expression in human cells. Together, VGX-3100 and the CELLECTRA™ device represent an integrated investigational product designed as a non-surgical treatment of HPV-16/18-related cervical HSIL (CIN2, CIN3) via an immune response directed against HPV-16/18. Further information about VGX-3100 is provided in the Investigator's Brochure.

1.1.10 ELECTROPORATION

VGX-3100 is delivered using the CELLECTRA™ *in vivo* electroporation (EP) device. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA vaccine which increases cell membrane permeability and improves the transfection of DNA and subsequent immunogenicity [25, 26]. Electroporation increases the uptake of plasmid DNA, thereby enabling increased expression and enhanced vaccine immunogenicity by 10 to 100 fold [27, 28]. 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 [29].

This study will use the CELLECTRA™ 2000 device which has been used in 26 trials with 3795 doses administered to human subjects as of September 30, 2016 with no significant safety issues identified. Further information about the CELLECTRA™ 2000 device can be found in the Investigator's Brochure and device User Manual.

1.1.11 IMIQUIMOD CREAM, 5%

Imiquimod Cream, 5% is a licensed product intended to be used in this study concomitantly with the investigational product and device. Imiquimod Cream, 5% will be centrally sourced, supplied in single-use packets (24 per box), each of which contains 250 mg of the cream, equivalent to 12.5 mg of imiquimod. The product manufacturer is Perrigo, Yeruham 80500, Israel.

1.1.12 STUDY RATIONALE

This pilot study is being conducted in a population with vulvar dysplasia using a randomized, open-label design to demonstrate the efficacy of VGX-3100 followed by EP in women with vulvar HSIL associated with HPV-16/18 either alone or in combination imiquimod. The overall aim is to determine if treatment with VGX-3100 could allow women with vulvar HSIL to avoid or minimize surgical treatment procedures. Proof of concept that VGX-3100 can induce resolution of both HPV-associated dysplastic lesions and the underlying HPV-16/18 infection was shown in a Phase 2b study of cervical intraepithelial neoplasia (CIN). The similar underlying pathogenic mechanisms between cervical and vulvar HSIL form the basis of the clinical hypothesis that VGX-3100 could be a non-surgical therapeutic option for the treatment of vulvar HSIL, which is a significantly under met medical condition. A VGX-3100 with imiquimod-administration study drug is also included, given the prevalent use of imiquimod as a topical medical treatment of vulvar lesions, to investigate if a more robust immune response is achieved with VGX-3100, to potentially increase regression of vulvar HSIL.

1.1.13 DOSE AND REGIMEN RATIONALE FOR VGX-3100

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 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 [30].

1.1.14 RATIONALE FOR IMIQUIMOD

Imiquimod cream is prescribed for the topical treatment of certain skin growths including external genital and perianal warts. Therefore, imiquimod may be able to be used synergistically with VGX-3100.

Randomized controlled trials have shown that the application of topical imiquimod 5% is effective for the treatment of vulvar HSIL although it is not approved by the US Food and Drug Administration for this purpose. Imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG). Published regimens include three times weekly application to affected areas for 12 – 20 weeks, with colposcopic assessment at 4-6 week intervals during treatment [17].

This study will include a study group to explore whether the efficacy of VGX-3100 is able to be enhanced by concomitant treatment with Imiquimod. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

1.1.15 INCLUSION OF WOMAN-PRO, CLINICAL TRIAL VERSION 2.0

The original WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) was developed by Beate Senn and colleagues [20,31,32] for use following post-surgical intervention. Development of the tool was aligned with the FDA PRO Guidance [33]and included a review of the literature as well as direct patient and expert input. Preliminary measurement properties were assessed in a cross-sectional study. However, despite rigorous development and promising initial measurement properties, gaps in the development and psychometric evaluation exist. To address these gaps, Inovio and collaborators initiated a small qualitative study to confirm the content validity of the tool and support a cross-cultural adaptation of the measure for use in a clinical trial setting of US English and US Spanish speaking subjects. The results of this research is the Clinical Trial of the WOMAN-PRO (2.0) which is utilized in this study.

The WOMAN-PRO Clinical Trial Version 2.0 is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The physical domain is comprised of 15 lesion-related symptoms and includes 5 additional items to measure impact in daily life. Psychosocial constructs are assessment through 11 items that address feelings, thoughts and limitations. Each item is scored using a 4-point Likert scale with higher scores indicating greater difficulty or severity. The recall period is the past week.Details are included in Section 6.8.

1.1.16 POTENTIAL RISKS OF INVESTIGATIONAL PRODUCTS

Based on the phase 1 and 2 clinical experience, the injection site reactions associated with the IM injection and electroporation are generally mild and limited to a few days in

duration at most. The full risk profile for VGX-3100 is described in the Investigator Brochure.

Local skin and application site reactions are the most frequently reported adverse reactions associated with topical imiquimod 5% treatment. Erythema, erosion, excoriation/flaking, edema, induration, ulceration, scabbing, and vesicles have been reported at the application site [34]. The full risk profile of imiquimod 5% treatment is available in the package insert and prescribing information.

1.1.17 POTENTIAL BENEFITS OF STUDY PARTICIPATION

This study has been designed to provide non-surgical treatment with the aim of avoiding the need for surgical excision or laser ablation, which can be disfiguring and have significant associated morbidity. In the absence of complete resolution of vulvar lesions, there would still be potential benefit from a partial response, which would minimize the amount of excisional therapy that may be needed. All currently accepted surgical treatments for VIN are associated with risks inherent with any surgical procedure including anesthesia, post-operative bleeding, infection, or damage to surrounding structures such as the clitoris, urethra, or anus. 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 of vulvar HSIL. Consequently, there is the potential to reduce the risk of recurrent disease.

2. HYPOTHESIS AND STUDY OBJECTIVES

Four 6 mg doses of VGX-3100 (DNA plasmids encoding E6 and E7 proteins of HPV-16 and HPV-18) delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA™ 2000 alone or in combination with imiquimod to adult women with histologically confirmed vulvar HSIL associated with HPV-16 and/or HPV-18 (HPV-16/18), will result in a higher percentage of women with regression of HSIL of the vulva based on histology (i.e. biopsies or excisional treatment) and virologic clearance of HPV-16/18 from vulvar tissue compared with historical control.

2.1 PRIMARY OBJECTIVE AND ENDPOINT

Objective	Endpoint
Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, with respect to combined histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue	Proportion of subjects with no histologic evidence of vulvar HSIL[5] and no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)[6].

2.2 SECONDARY OBJECTIVES AND ASSOCIATED ENDPOINTS

Secondary Objectives	**Associated Secondary Endpoints**
1. Evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod	1a. Local and systemic events for 7 days following each dose as noted in the Participant Diary. 1b. All adverse events including SAEs, AESI's, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)[4]
2. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL**	2. Proportion of subjects with **no evidence of vulvar HSIL[5]** on histology (i.e. biopsies or excisional treatment) at Week 48 visit
3. Determine the efficacy of four doses of VGX-3100, alone or in combination with imiquimod, as measured by **virologic clearance of HPV-16/18** in vulvar tissue	3. Proportion of subjects with **no evidence of HPV-16/18[7]** in vulvar tissue samples at Week 48 visit
4. Determine the efficacy of **VGX-3100,** alone or in combination with imiquimod, as measured by **histologic regression of vulvar HSIL to normal tissue**	4. Proportion of subjects with **no evidence of vulvar HSIL, no evidence of vulvar LSIL (VIN1), and no evidence of condyloma** on histology (i.e. biopsies or excisional treatment) at the Week 48 visit
5. Determine the efficacy of four doses of **VGX-3100,** alone or in combination with imiquimod, as measured by **non-progression of vulvar HSIL** to vulvar cancer as determined by histology	5. Proportion of subjects with **no progression[8]** of vulvar HSIL to vulvar cancer from baseline to Week 48 visit
6. Determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by **reduction in the surface area of the qualifying[9] vulvar lesion(s)**	6. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying lesion (s) at Week 48 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion size of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
7. Describe the **cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 4	7. Flow Cytometry response magnitudes at baseline and Week 27 visits
8. Determine the efficacy of four doses of VGX-3100 alone or in combination with imiquimod with respect to histopathologic regression of vulvar HSIL or viologic clearance of HPV-16/18 in vulvar tissue	8. Proportion of subjects with no histologic evidence of vulvar HSIL[5] or no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)

2.3 EXPLORATORY OBJECTIVES AND ASSOCIATED ENDPOINTS

Exploratory Objectives	**Associated Exploratory Endpoints**
1. Describe the efficacy of VGX-3100, administered alone or in combination with imiquimod, at **Week 74 and/or Week 96** as measured by reduction in the surface area of the qualifying[9] vulvar lesion(s), in subjects without a complete resolution at Week 48	1. Percent reduction in the cumulative surface area of the acetowhite vulvar lesion(s) as determined by the quantitative analysis of standardized pre-biopsy photographic imaging of the qualifying lesion (s) at Week 74 and/or Week 96 compared to baseline[10]. Results will be classified as: no clinically significant lesion resolution (reduction in lesion area of 0-25%), partial lesion area resolution (>25% and <100% reduction), and complete lesion resolution (no visible lesion).
2. Describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by **histologic regression** of vulvar HSIL	2. Proportion of subjects with no evidence of vulvar HSILon histology (i.e. biopsies or excisional treatment) at Week 74 for subjects who receive 5 doses of VGX-3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
3. Describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by **virologic clearance** of HPV-16/18	3. Proportion of subjects with **no evidence of HPV-16/18** in vulvar tissue samples at Week 74 and/or Week 96.
4. Evaluate **tissue immune responses** to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples	4. Assessment of pro-inflammatory and immunosuppressive elements in tissue[11]
5. Describe **virologic** clearance of HPV-16/18 from non-vulvar anatomic locations	5. Proportion of subjects who have cleared HPV-16/18 on specimens from non-vulvar anatomic locations without surgical intervention (inclusive of cervix, oropharynx, vagina and intra-anus) at Week 48 compared to baseline
6. Describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression	6. Vulvoscopy, HPV test results (vulvar swab and vulvar tissue) and miRNA profile (Day 0, Week 15 and 48) in conjunction with histologic regression of vulvar HSIL at Week 48 visit
7. Describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod	7. PRO endpoints will be obtained at Day 0 prior to first dose, Weeks 4, 12, 24 after dosing, and at Weeks 15, 27, 48, 52, 74, and Weeks 96, and 100 as applicable.

8. Describe the **humoral and cellular immune response** of VGX-3100 administered alone or in combination with imiquimod, post dose 3, post dose 4, and after additional dosing	8a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits 8b. Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits
9. Determine the long term efficacy of VGX-3100 alone or in combination with imiquimod with respect to histopathologic regression of vulvar HSIL or virologic clearance of HPV-16/18 in vulvar tissue	9. Proportion of subjects with no histologic evidence of vulvar HSIL[5] or no evidence of HPV-16/18 at Week 74 and 96 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment)

3. STUDY DESIGN

HPV-201 is a Phase 2, randomized, 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 delivered with CELLECTRA™ 2000 alone or in combination with imiquimod in adult women with histologically confirmed vulvar HSIL associated with HPV-16/18. Approximately 36 subjects will be enrolled. Twenty-four subjects will receive VGX-3100 alone and 12 subjects will receive VGX-3100 and topical imiquimod treatment. The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

Subjects are randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2) on Day 0, and (d) age category (<45 years vs. ≥45 years) on Day 0.

To be eligible for the study, subjects must sign consent to participate and have a vulvar punch biopsy/biopsies of approximately 4 mm with lesion remaining, and photographs of the acetowhite vulvar lesion(s) at the time of screening. In the case of multifocal disease, the two lesions that potentially contain the most advanced disease, as judged by the Investigator, should be chosen for biopsy using vulvoscopy and documented using standardized high resolution photography with a digital single-lens reflex (SLR) camera on the case report form. Biopsy slides will be sent to a PAC for evaluation prior to enrollment. In order to be eligible for enrollment, the PAC must assign the diagnosis of vulvar HSIL based on the biopsy sample(s). Subjects must also have a vulvar specimen 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, PRO instruments will be provided and will include the Short Form Health Survey version 2 (SF-36v2™), the EQ-5D-5L (EuroQol Research Foundation), WOMAN-PRO (WOMen with vulvar Neoplasia) Clinical Trial Version 2.0 and two additional PRO questions assessing quality of life after surgery or biopsy.

The total duration of the study is up to 10 weeks for the screening period, and 100 weeks for the treatment and follow-up periods. Amendment 5.0 reduces the study duration to 78 weeks for subjects not reaching the Week 78 visit at the time of the amendment

3.1 TREATMENT REGIMENS

All eligible subjects who consent to participate in the study will receive four doses of 6 mg of VGX-3100 administered by IM injection followed by EP. The first dose will be administered as soon as possible following confirmation of the HSIL diagnosis, HPV-16/18 status and all other eligibility criteria but no more than 10 weeks following collection of the subject's biopsy specimen used for diagnosis by the PAC.

Each dose of VGX-3100 will be administered in a 1 mL volume IM (deltoid preferred site, or the anterolateral quadriceps as an alternate site) followed immediately by EP with the CELLECTRA™ 2000 device. Figure 1 (Appendix A) shows the original study visit schedule, in which study subjects will receive at least 4 doses of VGX-3100 and potentially a 5th and 6th dose depending upon their disposition with regard to histologic and lesion area changes. Figure 1a shows the revised visit schedule per Protocol Amendment 5.0. In both schedules, the first dose will be administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose will be administered at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose at Week 52 per the judgment of the Investigator.

With Amendment 5.0, subjects will complete the study at Week 78 and will not be offered a 6th dose. Subjects who were beyond Week 78 at the time of IRB approval of Amendment 5.0, will return for their final visit at their next scheduled timepoint as outlined in Table 1. Subjects must sign the IRB-approved informed consent document for Amendment 5.0 prior to the initiation of procedures for their final study visit.

Imiquimod treatment – Participants who have been enrolled in the VGX-3100 with imiquimod study group will continue with study visits per protocol, but no further participants will be enrolled into this study group. Subjects randomized to the VGX-3100 with imiquimod study group will apply imiquimod 5% cream to the vulvar lesion beginning in the evening on Day 0, and will continue to apply treatment three times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing). Subjects unable to tolerate imiquimod treatment may reduce their dosing frequency, and will document their use on the imiquimod dosing log provided.

3.2 EFFICACY ASSESSMENT

The efficacy assessment will be based upon histopathology. Visualization of a normal appearing vulva by visual inspection with vulvoscopy is insufficient evidence to confirm disease regression. Disease regression will be based on histopathologic assessment at Week 48, 74, and at Week 96 for subjects reaching Week 96 prior to Amendment 5.0 or for whom that is the final visit. Subjects will be monitored during the course of the study by vulvoscopy. Lesion(s), defined as areas that stain acetowhite, will be assessed and photographed during vulvoscopy at Screening, Day 0, and Weeks 4, 12, 27, 48, 74, and at Week 96 for subjects who have reached this timepoint prior to Amendment 5.0 or for whom this is the final visit. Using standardized high resolution digital photographic imaging, vulvar lesion(s) will also be quantitatively measured at Screening, Day 0, and Weeks 48, 74, and at Week 96 for subjects who have reached that timepoint prior to Amendment 5.0 or for whom that is their final visit.

Biopsies obtained as part of the study at Screening will be from the region of most advanced disease as judged by the Investigator, and must be approximately 4 mm in

length. Visible lesion must remain after screening biopsy to ensure measurement on study. A qualifying lesion is defined as a vulvar lesion which is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening.

The decision process following results of the Week 48 biopsy are described in Figure 2 and are as follows: At Week 48, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesions as study start, from the region of most advanced disease based upon the judgment of the Investigator (see Table 2 for Minimally Required Biopsy Procedures).

If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Figure 2, Subgroups A or B), the subject will continue to Week 74 for vulvoscopy, and biopsy of the same lesion(s) as study start.

If after evaluation of the biopsy tissue HSIL remains, but there is a reduction in lesion size or no increase in lesion size from baseline (Figure 2, Subgroups C or D), the Investigator has the option to give the subject a 5th dose of VGX-3100 at Week 52, and the subject will continue on study with vulvoscopy and biopsy at Week 74. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

The decision process following results of the Week 74 biopsy for subjects who completed this visit prior to Amendment 5.0 are described in Figure 3 (Appendix B) for the original study design. The evaluation process following results of the Week 74 biopsy under Amendment 5.0 are described in Figure 3a and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as at study start Investigator(see Table 2). If, after evaluation of Week 74 biopsy tissue by the PAC, there is no evidence of HSIL (Subgroups A or B), the Investigator will use their clinical judgment regarding follow-up care of the subject (not part of study activities).

If, after evaluation of the biopsy tissue HSIL remains, but there is a reduction in the qualifying lesion(s) size or no change in lesion size from baseline (Subgroups C or D), the subject will receive further standard of care treatment (not part of study activities) per the Investigator's judgment.

The decision process for subjects who are beyond Week 78 at the time of IRB approval of Amendment 5.0 can be found in Appendix C. These subjects will complete the study at their next scheduled visit as outlined in Table 1. Subjects must sign the IRB-approved informed consent document for Amendment 5.0 prior to the initiation of procedures for their final study visit.

In the event of worsening disease prior to the end of the study (i.e., Subgroup E), the subject will receive surgical treatment per the Investigator's judgment and will continue on study with vulvoscopy, but without further study treatment or biopsy. In the event of worsening disease at the final visit, the subject will receive standard of care treatment (not part of study activities) per their treating physician. If wide excision is conducted at or prior to the subjects last on site visit, the sample obtained will be sent to the PAC for evaluation. For a finding of carcinoma, subjects will receive surgical treatment, and be discontinued from study treatment. The event will be reported as an SAE per section 7.1.4.

All visible lesions should be biopsied at Week 48. For subjects for whom Week 78 is their final visit, all visible lesions should be biopsied at Week 74. For subjects for whom the final visit is Week 96, all visible lesions should be biopsied at Week 96.

If there is a new lesion identified at evaluation, or a non-qualifying lesion that is rebiopsied and confirmed to be vulvar HSIL and HPV-16/18 positive at evaluation, a discussion will take place between the Medical Monitor and the Principal Investigator to determine if additional dosing at Week 52 is appropriate.

Table 2: Minimally Required Procedure at Biopsy Visit

Pre-biopsy Vulvoscopy Finding	Minimally required procedure
No acetowhite lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator; new lesions or lesions that did not qualify at baseline should be biopsied at evaluation.
Acetowhite Lesion	Vulvar punch biopsy and lesion photography; biopsy should be conducted of the same qualifying lesion as study entry from the region of potentially most advanced disease based upon judgment of the Investigator; new lesions or lesions that did not qualify at baseline should be biopsied at evaluation
Multiple acetowhite lesions	Vulvar punch biopsies and lesion photography; biopsy should be conducted of the same qualifying lesions as study entry from the region of potentially most advanced disease based upon judgment of the Investigator; new lesions or lesions that did not qualify at baseline should be biopsied at evaluation

3.2.1 DEFINITION OF RESPONDER AND NON-RESPONDER FOR THE PRIMARY ENDPOINT

A treatment responder is defined as a subject with no histologic evidence of vulvar HSIL and no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation and who did not receive any non-study related treatment for vulvar HSIL. A treatment non-responder is a subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation, or a subject with evidence of HPV-16/18 at evaluation, or a subject who received non-study related treatment for vulvar HSIL. Any case of histologically confirmed progression to carcinoma according to the PAC is considered a non-responder.

Responder and non-responder definitions (Table 3) take into account both histopathologic regression of vulvar HSIL and virologic (HPV-16/18) clearance from tissue samples since HPV persistence is an important factor in the clinical progression of HSIL.

Table 3: Definition of Responder and Non-responder for the Primary Endpoint	
Responder	**Non-Responder**
Subject with no histologic evidence of vulvar HSIL AND Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation OR Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

3.2.2 DEFINITION OF RESPONDER AND NON-RESPONDER FOR THE SECONDARY AND EXPLORATORY ENDPOINTS

Table 4: Definition of Responder and Non-responder for HSIL Regression Endpoint	
Responder	**Non-Responder**
Subject with no histologic evidence of vulvar HSIL AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation OR Subject who received non-study related treatment for vulvar HSIL

Table 5: Definition of Responder and Non-responder for Viral Clearance Endpoint	
Responder	**Non-Responder**
Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

Table 6: Definition of Responder and Non-responder for Complete HSIL Regression Endpoint	
Responder	**Non-Responder**
Subject with no histologic evidence of vulvar HSIL, LSIL (VIN1), or condyloma AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL, LSIL (VIN1), or condyloma at evaluation OR Subject who received non-study related treatment for vulvar HSIL

Table 7: Definition of Responder and Non-responder for Disease Non-Progression Endpoint	
Responder	**Non-Responder**
Subject with no histologic evidence of a worsening vulvar condition to vulvar cancer at Week 48 relative to baseline AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of worsening of vulvar condition to vulvar cancer at Week 48 relative to baseline OR Subject who received non-study related treatment for vulvar HSIL

Table 8: Definition of Responder and Non-responder for HSIL Regression or Viral Clearance Endpoint	
Responder	**Non-Responder**
Subject with no histologic evidence of vulvar HSIL OR Subject with no evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation AND Subject who did not receive any non-study related treatment for vulvar HSIL	Subject with histologic evidence of vulvar HSIL or vulvar carcinoma at evaluation AND Subject with evidence of HPV-16 or HPV-18 in vulvar tissue at evaluation OR Subject who received non-study related treatment for vulvar HSIL

3.3 SAFETY ASSESSMENT

Safety monitoring will include:

1) Local and systemic events for 7 days following each dose as noted in the Participant Diary

2) All adverse events including SAEs, AESIs, SUSARs, UADEs, and other unexpected AEs for the duration of the study.

All subjects will be followed through Week 78 under Amendment 5.0, or up to 100 weeks if beyond Week 78 at the time of Amendment 5.0.

3.3.1 DATA SAFETY & MONITORING BOARD

An independent Data Safety & Monitoring Board (DSMB) will provide safety oversight. The DSMB will meet quarterly to review safety data and regression/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 verified per protocol definition, further enrollment and study treatment will be halted until a thorough review has been conducted by the Medical Monitor, PI 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, 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 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, PI 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, 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.

3.4 IMMUNOGENICITY ASSESSMENT

The study explores humoral and cell mediated immune responses to VGX-3100 in blood samples taken at baseline (i.e., Screening and Day 0 prior to dosing) and Weeks 15, 27, 48, 74 and 96. Vulvar samples will also be analyzed for evidence of immune responses at Screening and Weeks 48, 74 and 96. Samples will not be obtained at Week 96 for subjects who complete the study prior to this timepoint, per Amendment 5.0.

3.5 VIROLOGIC ASSESSMENT

Tissue samples will be obtained to characterize vulvar HPV infection at Screening, Weeks 48, 74 and 96. Cervical samples, oropharyngeal (OP) rinse samples, vulvar, vaginal, and intra-anal tissue swab samples will be obtained to characterize HPV infection at the following time points: Day 0 prior to dosing (OP, cervical, vulvar, vaginal and intra-anal), Week 4 (Vulvar only), Week 12 (Cervical and Vulvar) and Weeks 27, 48, 74 and 96 (OP, vulvar, vaginal and intra-anal only). Samples will not be obtained at Week 96 for subjects who complete the study prior to this timepoint, per Amendment 5.0. At week 48 and 96, a cervical sample will also be collected.

4. SELECTION OF SUBJECTS

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in the study:

1. Must understand, agree and be able to comply with the requirements of the protocol. Subjects must be willing and able to provide voluntary consent to participate and sign a Consent Form prior to study-related activities;
2. Women aged 18 and above;
3. Vulvar infection with HPV types 16 and/or 18 confirmed by screening biopsy;
4. Vulvar tissue specimen/blocks must be collected within 10 weeks prior to anticipated date of first dose of study drug and have confirmed histologically confirmed vulvar HSIL by the Pathology Adjudication Committee at screening;

5. Must be judged by the Investigator to be an appropriate candidate for the protocol-specified procedure (i.e. excision or biopsy) required at Week 48;
6. Must have vulvar HSIL that is accessible for sampling by biopsy instrument and of adequate size to ensure that a visible lesion remains after an approximately 4 mm screening biopsy;
7. Must have vulvar HSIL that can be completely demarcated for area measurement;
8. Must meet one of the following criteria with respect to their reproductive capacity:
    a. Is post-menopausal as defined by spontaneous amenorrhea for more than 12 months or spontaneous amenorrhea for 6-12 months with FSH level >40 mIU/mL;
    b. Is surgically sterile due to absence of ovaries or due to a bilateral tubal ligation/occlusion performed more than 3 months prior to screening;
    c. Women of Child Bearing 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 6 months following the last dose of investigational product. Acceptable methods are the following:
        i. Hormonal contraception: either combined or progestin-alone including oral contraceptives, injectable, implants, vaginal ring, or percutaneous patches. Hormonal contraceptives must not be used in subjects with a history of hypercoagulability (e.g., deep vein thrombosis, pulmonary embolism);
        ii. Abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle;
        iii. Intrauterine device or intrauterine system;
        iv. Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject.
9. Normal screening electrocardiogram (ECG) or screening ECG with no clinically significant findings as judged by the Investigator.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. Untreated microinvasive or invasive cancer;
2. Biopsy-proven Vaginal Intraepithelial Neoplasia (VAIN) and are not undergoing medical care and/or treatment for VAIN;
3. Biopsy-proven Anal Intraepithelial Neoplasia (AIN) and are not undergoing medical care and/or treatment for AIN;
4. Biopsy-proven Cervical Intraepithelial Neoplasia (CIN) 2/3 and are not undergoing medical care and/or treatment for CIN;
5. Biopsy-proven differentiated VIN;
6. Vulvar HSIL that is not accessible for sampling by biopsy instrument;
7. Vulvar HSIL that is not of adequate size to ensure that a visible lesion remains after biopsy;

8. Treatment for genital warts within 4 weeks prior to screening;
9. Any previous treatment for vulvar HSIL (e.g. with surgery and/or imiquimod) within 4 weeks prior to screening;
10. Allergy to imiquimod 5% cream or to an inactive ingredient in imiquimod 5% cream for subjects enrolled prior to Protocol Amendment v3.0 (dated 26Mar2019);
11. Is pregnant, breastfeeding or considering becoming pregnant within 6 months following the last dose of investigational product;
12. Presence of any unresolved abnormal clinical laboratory values greater than Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 within 45 days prior to Day 0 **or** less than or equal to Grade 1 but deemed clinically significant by the Investigator;
13. Immunosuppression as a result of underlying illness or treatment including:
    a) History of or positive serologic test for HIV at screening;
    b) Primary immunodeficiencies;
    c) Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic, and ophthalmic corticosteroids are allowed);
    d) Current or anticipated use of disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate) and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept);
    e) History of solid organ or bone marrow transplantation;
    f) Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. History of previous therapeutic HPV vaccination (licensed prophylactic HPV vaccines are allowed, e.g. Gardasil®, Cervarix®);
15. Received any non-study related non-live vaccine within 2 weeks of each study dose;
16. Received any non-study related live vaccine (e.g. measles vaccine) within 4 weeks of each study dose;
17. Significant acute or chronic medical illness that could be negatively impacted by the electroporation treatment as deemed by the Investigator;
18. 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
    a) Chronic renal failure, angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias;
    b) Treatment for non-anogenital malignancy within 2 years of screening, with the exception of superficial skin cancers that only require local excision;
    c) 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;

d) History of seizures unless seizure free for 5 years with the use of one or fewer antiepileptic agents;

e) 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;

f) Resting heart rate <50 bpm (unless attributable to athletic conditioning) or >100 bpm at Screening or Day 0;

g) Prior major surgery within 4 weeks of Day 0;

19. Participated in an interventional study with an investigational compound or device within 4 weeks of signing informed consent (participation in an observational study is permitted);

20. 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 (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);

21. Vulnerable populations:

a) Active drug 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 service personnel who have the potential to be relocated;

d) Study-related staff or family members of study-related staff;

22. Any illness or condition that in the opinion of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF STUDY SUBJECTS

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Subjects who manifest a Grade 4 toxicity attributable to the study treatment will be discontinued from the study treatment. Subjects will not receive further study treatment/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 study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that subject.

4.3.2 CRITERIA FOR WITHDRAWAL FROM THE STUDY

All subjects who begin treatment should be encouraged to complete all phases of the study, including those who discontinue treatment. A subject may voluntarily withdraw from study participation at any time. A subject may be withdrawn at any time at the discretion of the Investigator for any maternal obstetrical or medical complications after consultation with the medical monitor.

Subjects who become ineligible to continue on study based on no longer meeting exclusion criteria should be discontinued from study treatment, managed per routine standard of care and should continue on study without further biopsy.

Subjects who are withdrawn from study participation after starting treatment will not be replaced. Reasons for study withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source document.

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 VIN, 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 she 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 she 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 1). At a minimum, the Investigator should make every effort to have the subject complete all assessments designated for the discharge visit, Week 100 for subjects completing the study prior to Amendment 5.0.

For subjects completing the study under Amendment 5.0, the discharge visit will be Week 78 unless the subject was beyond Week 78, then the discharge visit will be the next scheduled visit per the schedule of events. The updated consent for Amendment 5.0 must be obtained before final visit procedures are performed. For subjects completing the study at Week 78, the repeat cervical colposcopy will be performed at Week 74 or the discharge visit. The socio-behaviorial assessment scheduled for Week 100 will be done at the final discharge visit for subjects completing the study before Week 100. A subject will be considered to have completed the study when all scheduled study treatments and follow-up visits are completed.

4.3.3 SPONSOR NOTIFICATION OF DISCONTINUATION/WITHDRAWAL

The Investigator or study coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an AE. If a subject discontinues from the study or is withdrawn from the study prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. The Investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events in the synopsis, Table 1. Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1.

4.3.4 REASON FOR DISCONTINUATION/WITHDRAWAL

The primary reason for a subject discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories and recorded on the 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
- 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 the subject. Investigator must consult the medical monitor before withdrawing a subject from participation in the study.
- Protocol violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after at least 3 repeated attempts including letter sent by certified mail or equivalent.

5. STUDY TREATMENT

5.1 INVESTIGATIONAL PRODUCTS

The VGX-3100 drug product contains DNA plasmids for expression of HPV-16 E6/E7 (pGX3001) and HPV-18 E6/E7 (pGX3002) antigens that have been designed and constructed using proprietary synthetic consensus DNA (SynCon™) technology. The VGX-3100 formulation to be used in this study is described in Table 9 and will be presented in a clear glass vial for intramuscular injection.

Imiquimod 5% is a topical cream for external use and is supplied in single-use packets containing 250 mg of cream. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. Inactive ingredients include benzyl alcohol, cetyl alcohol, glycerin, methylparaben, oleic acid, oleyl alcohol, polysorbate 60, propylparaben, purified water, stearyl alcohol, sorbitan monostearate, white petrolatum, and xanthan gum. There are 24 single-use packets of imiquimod in one box. The product manufacturer is Perrigo, Yeruham 80500, Israel.

Imiquimod is indicated for the treatment of external genital and perianal warts/condyloma acuminate in patients 12 year old or older. Although it is not approved by the US Food and Drug Administration for the treatment of vulvar HSIL, imiquimod is currently recommended as a non-surgical, off-label treatment option for vulvar dysplasia by the American College of Obstetricians and Gynecologists (ACOG).

VGX-3100 and imiquimod will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 9. Investigational Products

Product	Formulation	Dose
VGX-3100	6 mg (1:1 mix of SynCon™ HPV-16 E6/E7 and HPV-18 E6/E7 plasmids) in 150 mM sodium chloride and 15 mM sodium citrate	1 mL
Imiquimod Cream, 5%	12.5 mg imiquimod per 250 mg single-use packet	250 mg

5.2 PACKAGING AND LABELING

5.2.1 PACKAGING AND LABELING OF VGX-3100 AND IMIQUIMOD

Each vial of VGX-3100 will be labeled with a single-panel label that will include, at a minimum, the information in Figure 5. The actual product label names the product as VGX-3100X; the "X" designation was included to differentiate the current buffer formulation from a previous formulation of VGX-3100 in water. Imiquimod Cream, 5% will have both the original manufacturer's label on individual packets and the back of the carton, and an investigational label on the front of the carton. The labels will contain, at minimum, the information shown in Figure 6.

Figure 5. Example Labels for VGX-3100

SynCon™ VGX-3100 [6 mg/mL] 1 mL/Vial Single Use Vial Date of Manufacture: _____ Expiry Date: _____ Refrigerate at 2-8°C CAUTION: NEW DRUG - LIMITED BY FEDERAL LAW TO CLINICAL TRIAL USE ONLY Inovio Pharmaceuticals, Inc.

Figure 6. Example labels for imiquimod

Box (secondary package)
Study ID Imiquimod Cream, 5% **Composition:** One 0.25 g single-use packet contains: Imiquimod 12.5 mg Store at 4 – 25°C (39-77°F). Avoid freezing. For Dermatologic Use Only. Not for Ophthalmic Use. Keep out of reach of children. This package is not child resistant. CAUTION: New Drug - Limited by United States Law to Investigational Use Inovio Pharmaceuticals, Inc.

5.3 HANDLING AND STORAGE

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, VGX-3100 will be shipped in a refrigerated condition with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range for any product, the Sponsor, or its designee should be contacted immediately.

Upon arrival, VGX-3100 should be transferred from the shipping container into 2–8 °C (36-46 °F) storage, in a secure area, according to local regulations. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

Imiquimod will be shipped and stored at room temperature (4 – 25°C) according to the manufacturer's instructions. Avoid freezing.

5.4 PREPARATION AND DISPENSING

5.4.1 DISPENSING OF VGX-3100

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.

VGX-3100 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. The designated staff member will be responsible for dispensing the appropriate volume (1mL) of VGX-3100. No mixing or dilutions will be required.

VGX-3100 should be removed from the refrigerator and brought to room temperature. The product must be used within 4 hours of removal from the refrigerator. All material removed from the refrigerator must not be re-refrigerated.

Detailed instructions on handling and dispensing of VGX-3100 are provided in the Pharmacy Manual.

5.4.2 DISPENSING AND USE OF IMIQUIMOD

It is the responsibility of the Investigator to ensure that imiquimod labeled for study use is only dispensed to study subjects. It must be dispensed from official study sites only, by authorized personnel according to local regulations. Subjects will be given 1 box of imiquimod (24 single-use packets per box) at Day 0, one box at Week 4, and one box at Week 12. Subjects will be instructed to apply imiquimod externally to the vulvar lesion 3x per week prior to normal sleeping hours, for 20 weeks. Imiquimod should be left on the skin for 6 – 10 hours and then removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday application prior to sleeping hours. In the event that Imiquimod is not tolerated at 3 times per week, alternative administration approaches must be discussed and approved by the medical monitor.

Subjects will be provided with an imiquimod dosing log to record their use during the 20 week treatment period. The imiquimod dosing log should be brought to the clinic with the used imiquimod box, at Week 4, 12, and 24 for review with study personnel.

5.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current record of investigational product is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable

5.6 RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP must be returned to Inovio Pharmaceuticals, Inc., or its designee, if not authorized by Inovio Pharmaceuticals, Inc. to be destroyed at the site.

All IP returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor or by the authorized site representative if the Study Monitor is not present.

If IP(s) are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. Reconciliation of any unused IP must be performed and provided to the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor for review prior to on-site destruction.

5.7 USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA™ 2000 device are located in the User Manual. Each clinical site will receive training for the use of the CELLECTRA™ 2000 device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

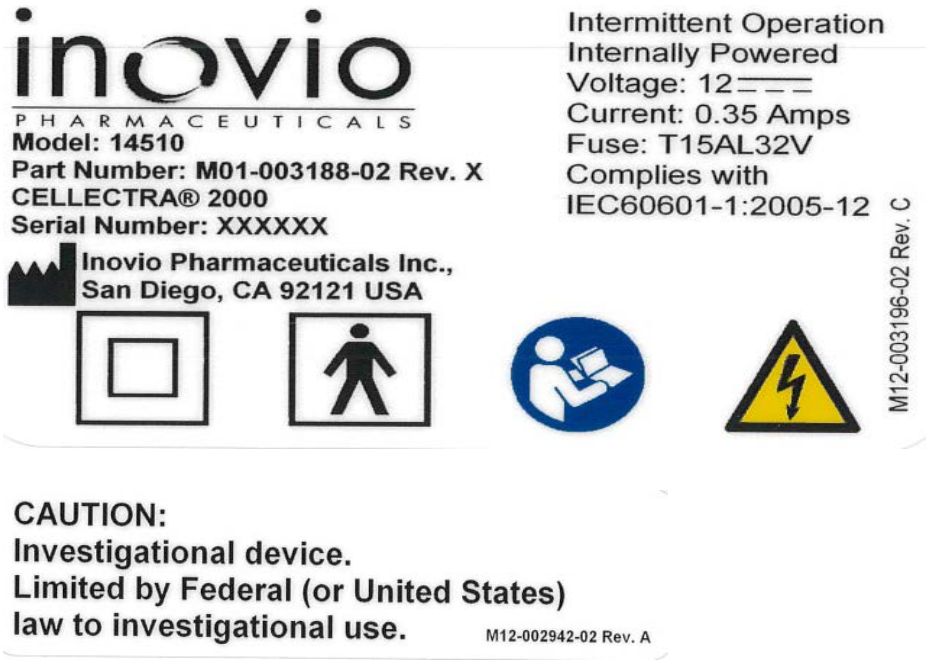
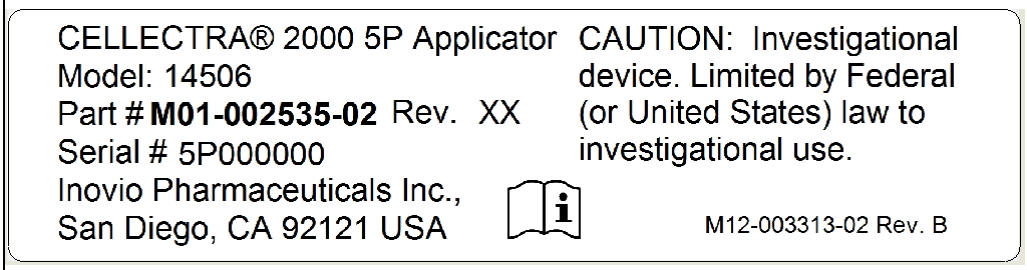
The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 Pulse Generator has a unique serial number, and each CELLECTRA™ 2000 Applicator has a unique serial number. Each CELLECTRA™ 2000 Array has a Lot Number, Manufacture Date, and Expiration Date.

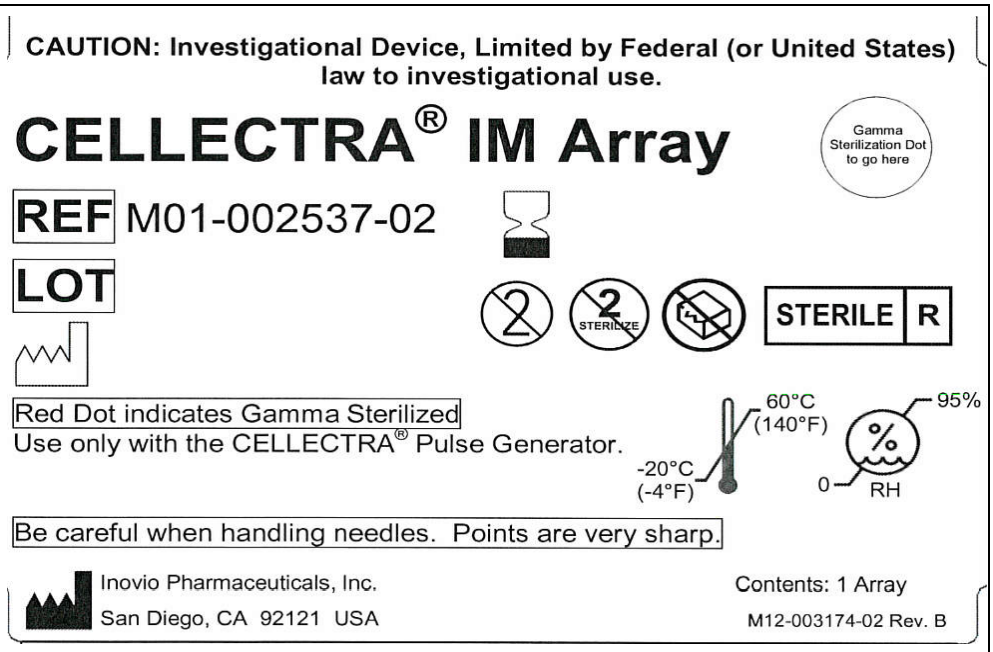
The treatment procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g. MD, DO, RN) in addition to successfully completing device training from sponsor personnel.

5.8 PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels in Table 10 below are presented as examples. *Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record investigational product accountability during study conduct.*

Table 10. Example Labels for the CELLECTRA™ 2000 Device (Pulse Generator, Applicator and Array)

Device Component	EXAMPLE Label
CELLECTRA™ 2000 Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA™ 2000 5P Applicator Model 14506 Part Number: M01-002535	

CELLECTRA™ IM Array REF: M01-002537	

5.9 INVESTIGATIONAL DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining investigational device and accountability logs. The device must have full traceability from the receipt of the products through the subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational product. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 2000 serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.10 RETURN AND DESTRUCTION OF INVESTIGATIONAL DEVICES

Upon completion or termination of the study, an Inovio representative will provide instructions regarding which materials should be destroyed onsite, and/or returned to Inovio Pharmaceuticals, Inc.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by an Inovio representative.

If product is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6. STUDY PROCEDURES AND TREATMENTS

This section lists the procedures and parameters for each planned study evaluation. The timing of each assessment is listed in the Schedule of Events Table (see Table 1).

A subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study specific procedures are performed.

Protocol waivers or exemptions will not be granted with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Events Table are essential and required for study conduct.

6.1 BEFORE TREATMENT PROCEDURES

6.1.1 SCREENING EVALUATIONS

Subjects who consent to participate and have paraffin-embedded tissue block(s) from vulvar tissue samples (formalin fixed tissue) from a previous biopsy, can have the samples sent to the central pathology lab for review by the PAC to assess eligibility. There will be a maximum allowable window of 10 weeks from the date of collection of the qualifying biopsy sample(s) (i.e. samples reviewed by PAC with HSIL consensus diagnosis), until the date of first study treatment (i.e. Day 0).

For those individuals diagnosed with vulvar 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.

Subjects must have a diagnosis of histologic vulvar HSIL confirmed by the PAC at screening, and a screening vulvar specimen test positive for HPV-16 and/or HPV-18 by PCR to be eligible for randomization into the study (provided the subject also meets other eligibility criteria). Subjects whose vulvar specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV-16 and/or HPV-18.

The assessments during the screening period will determine the subjects'' eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments.

The following screening evaluations will be performed within 10 weeks and up to 1 day prior to dosing on Day 0, except for 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.

- Signed informed consent

- Medical history/demographics, including history of prior vulvar HSIL and vulvar excisions
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Prior/concomitant medications review
- Determination of eligibility per inclusion/exclusion criteria
- Physical Exam (a full physical exam is mandatory at Screening)
- Vital signs (including body temperature, respiratory rate, blood pressure and heart rate), and height, weight and BMI measurements
- 12-lead ECG **within 45 days prior to Day 0**
- Baseline laboratory evaluations (includes complete blood count [CBC], serum electrolytes, blood urea nitrogen [BUN], creatinine, glucose, alanine aminotransferase [ALT], creatine phosphokinase [CPK], and urinalysis) to be performed **within 45 days prior to Day 0**
- Urine Pregnancy test
- Serology (HIV Ab)
- Whole blood and serum for baseline immunologic assay
- Vulvoscopy
    - Screening vulvoscopy is optional if vulvoscopy was performed upon collection of initial biopsy and corresponding lesion photography is available.
- Vulvar Lesion Photography
    - Photograph of the vulvar lesion(s) must be collected prior to and after biopsy at screening
    - If a **historical biopsy** sample is used to determine eligibility at screening and a pre-biopsy photograph is not available, a post biopsy photo will be sufficient.
- Biopsy:
    - Slides from all excised tissue must be reviewed by the PAC.

6.2 DURING TREATMENT PROCEDURES BY VISIT

Once eligibility has been confirmed, the subject will be randomized to receive study treatment. Visit dates and windows must be calculated from Day 0.

6.2.1 DAY 0

The following evaluations will be performed on Day 0 **prior to study treatment**:

- Determination of eligibility per Inclusion/Exclusion Criteria
- Review of concomitant medications and adverse events

- Randomization
- Patient Reported Outcomes
- Targeted physical assessment
- Vital signs
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

Study treatment will be administered and the following evaluations will be performed on Day 0 **after study treatment**:

- Post treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary (PD)
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device

6.2.2 8-14 DAYS POST DOSE 1 PHONE CALL

- Review Adverse Events
- Patient Reported Outcomes
- Review Day 0 PD
    - After completing a review of PD 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.

6.2.3 WEEK 4 (± 7 DAYS)

The following study evaluations will be performed at Week 4 **prior to study treatment**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs

- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Vulvar swab
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

The following study evaluations will be performed at Week 4 **after study treatment:**

- Post treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log (for subjects in the imiquimod arm)

Download EP data from device

6.2.4 8-14 DAYS POST DOSE 2 PHONE CALL

- Review Adverse Events and concomitant medications
- Patient Reported Outcomes
- Review Week 4 PD
  - After completing a review of PD 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.

6.2.5 WEEK 12 (± 7 DAYS)

The following study evaluations will be performed at Week 12 **prior to study treatment:**

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod arm
- Urine pregnancy test
- Cervical cytology and ThinPrep® for cervical HPV type
  - Collect menstrual cycle status and recent gynecologic history
- Vulvar swab
- Vulvoscopy

- Vulvar lesion photography of the qualifying lesion(s)

The following study evaluations will be performed at Week 12 **after study treatment:**

- Post-treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD
- Distribute 1 box of imiquimod and the imiquimod dosing log to subjects in the imiquimod arm

Download EP data from device

6.2.6 WEEK 15 (± 7 DAYS)

The following study evaluations will be performed at Week 15:

- Review Adverse Events and concomitant medications
- Review Week 12 Participant Diary
- Patient Reported Outcomes
- Whole blood and serum for immunologic assay including miRNA profile

6.2.7 WEEK 24 (± 7 DAYS)

The following study evaluations will be performed at Week 24 **prior to study treatment**:

- Review of concomitant medications and adverse events
- Review imiquimod dosing log and usage (accountability of returned product) for subjects in the imiquimod study group
- Targeted physical assessment
- Vital signs
- Urine pregnancy test

The following study evaluations will be performed at Week 24 **after study treatment:**

- Post-treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Patient Reported Outcomes
- Distribute PD

Download EP data from device

6.2.8 WEEK 27 (± 7 DAYS)

The following study evaluations will be performed at Week 27:

- Review of concomitant medications and adverse events
- Review Week 24 Participant Diary
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)

6.2.9 WEEK 38 PHONE CALL

- Review concomitant medications and adverse events

6.2.10 WEEK 48 (± 7 DAYS)

The following study evaluations will be performed at Week 48:

- Targeted physical assessment
- Vital signs
- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Urine pregnancy test
- Whole blood and serum for immunologic assay including miRNA profile
- Cervical cytology and ThinPrep® for cervical HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Vulvoscopy

- Vulvar lesion photography (pre-and post biosy), and quantitative measurement (pre-biopsy) of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.11 WEEK 52 (± 14 DAYS)

Subjects will have a Week 52 consultation to discuss their biopsy results and treatment plan. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test (for subjects receiving a 5th dose only)

Subjects receiving a 5th dose will have the following evaluations performed at Week 52 **after study treatment:**

- Post-treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device

6.2.12 WEEK 74 (± 14 DAYS)

The following study evaluations will be performed at Week 74:

- Review of concomitant medications and adverse events
- Review Week 52 Participant Diary for subjects receiving a 5th dose
- Targeted physical assessment
- Vital signs
- Patient Reported Outcomes
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- OP oral rinse, vulvar, vaginal and intra-anal swabs
- Cervical colposcopy (for subjects ending the study at Week 78 per Amendment 5.0)
- Vulvoscopy

- Vulvar lesion photography (pre-and post biosy), and quantitative measurement (pre-biopsy) of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.13 WEEK 78 (± 14 DAYS)

Subjects will have a Week 78 consultation to discuss their biopsy results and treatment plan. This will be the final visit for subjects reaching this timepoint under Amendment 5.0, and may occur via phone. The following assessments will also be performed:

- Review of concomitant medications and adverse events
- Targeted physical assessment (or full physical exam for subjects completing the study in-person at Week 78)
- Vital signs (for in-person visit only)
- Urine pregnancy test (for subjects receiving a 6th dose prior to Amendment 5.0 only)
- Socio-behavioral evaluation (for subjects completing the study at Week 78 per Amendment 5.0)

Subjects receiving a 6th dose will have the following evaluations performed at Week 78 **after study treatment:**

- Post-treatment AEs including injection site reaction assessment within 30-45 minutes after study treatment
- Distribute Participant Diary

Download EP data from device

6.2.14 WEEK 96 (± 14 DAYS)

The following study evaluations will be performed at Week 96 for subjects who have reached this timepoint before Amendment 5.0, or for whom this will be the final visit:

- Review of concomitant medications and adverse events
- Review Week 78 Participant Diary for subjects receiving a 6th dose prior to Amendment 5.0
- Targeted physical assessment (or full exam for subjects completing the study at Week 96)
- Vital signs
- Patient Reported Outcomes

- Socio-behavioral evaluation (for subjects completing the study at Week 96 per Amendment 5.0)
- Urine pregnancy test
- Whole blood and serum for immunologic assay
- Cervical colposcopy
    - Photographs during colposcopic examinations of the vagina and/or cervical areas should be obtained if lesions are identified.
- Cervical cytology and ThinPrep® for HPV type
    - Collect menstrual cycle status and recent gynecologic history
- OP oral rinse, vulvar, vaginal and intra-anal swabsVulvoscopy
- Vulvar lesion photography of the qualifying lesion(s)
- Vulvar biopsy or wide excision as per Investigator discretion:
    - All biopsy samples must be sent to the PAC for review

6.2.15 WEEK 100 (± 14 DAYS)

The following study evaluations will be performed at Week 100 for subjects who have reached this timepoint before Amendment 5.0 or for whom this will be the final visit:

- Review of concomitant medications and adverse events
- Socio-Behavioral Assessment; including self-reported smoking history, self-reported exposure to second-hand smoke, self-reported alcohol intake history, contraceptive history
- Full physical assessment
- Vital signs
- Urine pregnancy test

6.3 EVALUATIONS AND PROCEDURES

6.3.1 INFORMED CONSENT

All subjects must sign the informed consent prior to any study related procedures being performed (i.e., prior to any screening activities). The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures, in a language understandable to the subject. Explanation of the study includes, but is not limited to, study objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the

subject. The qualified study personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.3.2 RESCREENING OF SCREEN FAILURES

Subjects who sign the informed consent and are assigned a subject identification number (SID) but do not meet the eligibility criteria or fall outside of the screening window will be considered screen failures. If the Investigator believes rescreening is warranted, the Investigator must contact the medical monitor to discuss.

6.3.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique SID, which identifies the subject for all study-related procedures. SIDs are a combination of a up to two alpha letters study code, two alpha letter Country code, two digit site number, plus 3-digit subject number starting with 001 (e.g., VNUS01001). Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date must be documented on a Screening log/system and in the Interactive Response Technology (IXRS).

Subjects meeting eligibility criteria will be randomized by a computer generated allocation schedule.

6.3.4 SAFETY EVALUATIONS

6.3.4.1 PHYSICAL EXAMINATION

A full physical examination (PE) will be conducted during screening and study discharge unless otherwise indicated. 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. 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.

6.3.4.2 VITAL SIGNS

Vital signs will be measured at specified visits and will include:

- Sitting systolic and diastolic blood pressures with subject sitting at rest for at least 5 minutes before measurement
- Respiration rate
- Heart rate
- Oral temperature measured with an automated thermometer

6.3.4.3 WEIGHT AND HEIGHT

Weight will be measured at all dosing visits and at screening, and height will be measured at screening to assess BMI.

6.3.4.4 MEDICAL HISTORY

Medical history, including smoking history and gynecologic history, will be obtained at screening. All relevant (as judged by the Investigator) past and present conditions, as well as prior surgical procedures will be recorded for the main body systems.

6.3.4.5 SOCIO-BEHAVIORAL ASSESSMENT

Socio-Behavioral Assessment, including self-reported smoking history, self-reported history of exposure to second-hand smoke, self-reported alcohol intake history, self-reported recreational drug use history, self-reported history of contraceptive use and type of contraceptive if known, reproductive history, history of prior cervical dysplasia, and pregnancy history will be obtained at Screening.

At Weeks 48 and 100, socio-behavioral assessment will be performed to document any change from screening. Subjects who complete the study before Week 100 per Amendment 5.0, will have a socio-behavioral assessment completed at their final discharge visit

6.3.4.6 LABORATORY EVALUATIONS

At screening, blood samples will be taken to be tested for serum chemistry and hematology.

Complete blood count (CBC):

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hemoglobin, Hematocrit
- Platelet count

Serum Chemistry:

- Glucose
- Alanine aminotransferase (ALT)
- Blood urea nitrogen (BUN)
- Creatinine
- Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)
- Creatine Phosphokinase (CPK)

Urinalysis (UA):

Urine samples will be tested at screening by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose ≥ 1+) a microscopic examination should be performed.

6.3.4.7 PREGNANCY TESTING

For subjects of reproductive potential, a negative spot urine pregnancy test is required at screening, and prior to each study treatment, vulvoscopy and surgical excision or biopsy.

6.3.4.8 ELECTROCARDIOGRAM (ECG)

A single 12-lead ECG will be obtained during Screening after the subject has been in a supine position for 10 to 15 minutes. The ECG should include measurements of ventricular rate, PR, QRS, QRS axis, QT, QT_{cb} or QT_{cf}, ST segment, T wave as well as an Investigator assessment of whether the ECG is normal or abnormal (automated interpretations of ECG should not be used). Abnormal ECGs should be interpreted as "clinically significant (CS)" or "not clinically significant (NCS)" by the Investigator.

6.3.4.9 POST-TREATMENT REACTION ASSESSMENTS

The PD will capture subject reported local and systemic events for 7 days after the study treatment.

The subject will be provided a PD and will be asked to record the following the evening of study treatment through Day 6:

- Oral temperature and time taken (before 11:59 pm)
- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PD will be reviewed with the subject and research staff at 8 -14 Days post-dose.

The study staff will review the PD for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse event accordingly.

6.3.4.10 IMIQUIMOD DOSING LOG

Subjects randomized to the imiquimod arm, will record the dates of imiquimod application on the imiquimod dosing log during the 20 week treatment period. Subjects will contact site study personnel to report any adverse events and will return the log at their next visit.

6.4 INJECTION AND ELECTROPORATION (EP)

Subjects will receive four doses of VGX-3100 (6 mg DNA/dose) in a volume of 1 mL by intramuscular injection in the deltoid or lateral quadriceps muscles (preferably deltoid) followed immediately by EP with the CELLECTRA™ 2000. 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. Any device implanted in the chest (e.g., cardiac pacemaker, defibrillator or retained leads following device removal) excludes the use of the deltoid muscle on the same side of the body. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration at Weeks 4, 12, 24, and at Weeks 52 and 78 for Subgroups C and D only.

6.4.1 RISKS OF TREATMENT PROCEDURES

6.4.1.1 RISKS OF TREATMENT PROCEDURES TO VGX-3100

No serious related adverse events to VGX-3100 have been observed in the clinical trial experience to date. A summary of potential risks of IM Administration followed by EP with CELLECTRA™ can be found in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.1.2 RISKS OF TREATMENT PROCEDURES TO IMIQUIMOD

Adverse events reported in clinical trials with imiquimod cream, 5% for external genital warts can be found in the imiquimod product label [35], and in the VGX-3100 + Imiquimod Investigator's Brochure.

6.4.2 MANAGEMENT OF ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURE

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam), or equivalent, for anxiety related to the treatment procedure. Mild sedatives may be administered approximately 1 hour prior to study treatment. 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. acetaminophen, ibuprofen, ketorolac) before or after injection/EP.

Subjects who are allergic to or have contraindications to EMLA, acetaminophen, ibuprofen, ketorolac or a mild sedative may be offered a suitable alternative.

Medication taken for anxiety or pain management EMLA cream or sedatives should be added to the concomitant medications.

6.5 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry, hematology and serology assessments as well as urine pregnancy testing at Screening for inclusion into the study as listed in section 6.3.4.6.

6.6 ASSESSMENT OF CLINICAL STUDY ADVERSE EVENTS

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 PD which will be reviewed with study personnel at 8 – 14 days after dose 1 and 2, and at Weeks 15, 27, 74, and 96.

An assessment will be conducted at each visit during which subjects will be queried regarding the occurrence of any adverse events, concomitant medications new onset illness or disease, as well as contraceptive compliance. Subjects will be reminded to contact study personnel and immediately report any event that happens for the duration of the study. Unsolicited adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the subject's CRF.

6.7 ASSESSMENT OF INJECTION SITE REACTIONS

When evaluating injection site reactions throughout the study, the Investigator will be instructed to use the following grading scale:

Table 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

6.8 ASSESSMENT OF PATIENT REPORTED OUTCOMES

To assess quality of life and related impacts on subjects, patient-reported outcomes (PRO) instruments will be provided. Administration of PRO instruments will be performed according to the validated or otherwise developed procedures and instructions of each respective instrument. PROs will not be completed at Week 96 or 100 for subjects who complete the study prior to those timepoints per Amendment 5.0. The following PRO questionnaires will be used:

1. **WOMAN-PRO (WOMen with vulvAr Neoplasia PRO) Clinical Trial Version – 2.0** (Beate Senn; version modified by Inovio Pharmaceuticals and RTI Health Solutions): is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN. The recall period is the past week.[20].

   The WOMAN-PRO will be administered on paper only and should be the **first PRO instrument administrated** (i.e. before all other PROs) at each of the following time points:

   - Day 0 (*before* the first study treatment)
   - 8-14 days post dose 1
   - Week 4 (after study treatment)
   - 8-14 days post dose 2
   - Week 12 (after study treatment)
   - Week 15
   - Week 24 (after study treatment)
   - Week 27
   - Week 48 (after biopsy or surgical excision)
   - Week 74 (after biopsy or surgical excision)
   - Week 96 (after biopsy or surgical excision)
   - Week 100

2. **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) [36]. SF-36v2™ will be administered at the following time points:

   - Day 0 (*before* the first study treatment)
   - 8-14 days post dose 1
   - 8-14 days post dose 2
   - Week 48 (after biopsy or surgical excision)
   - Week 100

3. **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) [37, 38] and will be administered as described below:
    - Day 0 (*before* the first study treatment)
    - 8-14 days post dose 1
    - Week 4 (after study treatment)
    - 8-14 days post dose 2
    - Week 12 (after study treatment)
    - Week 15
    - Week 24 (after study treatment)
    - Week 27
    - Week 48 (after biopsy or surgical excision)
    - Week 74 (after biopsy or surgical excision)
    - Week 96 (after biopsy or surgical excision)
    - Week 100
4. **Additional Global PRO Questions** – regarding quality of life after surgery or biopsy. These two questions will be administered on paper at Week 52 only.

6.9 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 15, 27, 48, 74, and at Week 96 for subjects who complete that timepoint prior to Amendment 5.0. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

A standardized binding ELISA may be performed to measure the anti–HPV-16/18 antibody response induced by VGX-3100.

PBMCs will be isolated from whole blood samples. Assessment of cellular immune activity may occur via the application of the Interferon-γ enzyme-linked immunosorbent spot (IFN-γ ELISpot) assay as well as flow cytometry.

Additional assessment of cellular immune activity may occur via the application Flow Cytometry for the purposes of performing a Lytic Granule Loading Assay. The Lytic Granule Loading assay may examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD137, CD38 and CD69 (T cell activation markers) as well as PD-1 (exhaustion/activation marker). The Lytic Granule Loading assay may additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). Markers examined in this assay may change as new relevant data become available.

Profiling of miRNA will occur using plasma obtained at Day 0, Week 15 and 48. Assessment of Day 0 samples alone will explore predictive algorithms for response to treatment with VGX-3100 prior to dosing. Assessment of Week 15 and 48 samples will

be done as a comparison against Day 0, in order to look for changes in miRNA profiles that occur once dosing with VGX-3100 has begun, to explore construction of an algorithm to predict treatment success with VGX-3100.

6.10 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue or additional slides in the paraffin block after HPV genotyping and histologic diagnoses have been rendered at Screening, Weeks 48, 74 and 96 (for subjects who have a Week 96 biopsy visit), then unstained slides and/or the relevant paraffin blocks may be collected for assessment of pro-inflammatory and immunosuppressive elements in tissue, where feasible. Slides will be scanned for visualization of pathology changes.

Assessment of markers may include, but are not limited to, $CD8^+$ and $FoxP3^+$ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available.

6.11 VULVAR HPV TESTING

At Screening, Weeks 48, 74, and 96, a vulvar punch biopsy sample of approximately 4 mm will be obtained and sent to a central laboratory for HPV genotyping by PCR. Samples will not be obtained at week 96 on subjects who complete the study prior to that timepoint per Amendment 5.0.

In the case of multifocal disease, a vulvar biopsy of approximately 4 mm will be obtained from two lesions that potentially contain the most advanced disease as judged by the Investigator. The subject will be requested to abstain from sexual activity and refrain from use of douching to eliminate potential interference with the results of HPV testing.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of vulvar punch biopsy to eliminate potential interference with the results of HPV testing.

6.12 COLPOSCOPY, PAP SMEARS AND HPV TESTING

Cervical colposcopy will be performed at Day 0 and at Week 96 for subjects completing the study prior to Amendment 5.0. Subjects completing the study at Week 78 per Amendment 5.0 will have the repeat cervical colposcopy performed at Week 74 or discharge. Photographs of the cervix should be obtained if lesions are identified.

Pap smears will be obtained using ThinPrep® test kits at Day 0, Weeks 12, 48 and 96, and read in a central laboratory. Samples will not be obtained at Week 96 on subjects who complete the study prior to that timepoint, per Amendment 5.0.

HPV PCR will be performed on the ThinPrep® specimen. At each of these visits, menstrual cycle status & recent gynecologic history will be collected. If the Pap smear result suggests progression to cancer the Investigator may schedule an ad hoc visit to perform a colposcopy and possible biopsy if clinically indicated.

The subject will be requested to abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep® samples to eliminate potential interference with the results of HPV testing.

6.13 VULVOSCOPY, PHOTOGRAPHS, AND BIOPSIES

Eligible subjects are enrolled in the study based on the diagnosis of vulvar HSIL confirmed by the PAC. Subjects will undergo vulvoscopy to identify the lesion(s). Interval vulvoscopies will be performed at Day 0, Weeks 4, 12, 27, 48, 74, and at Week 96 for subjects completing Week 96 prior to or under Amendment 5.0. Vulvoscopic visualization of a normal appearing vulva is insufficient evidence to confirm disease regression. An additional visit may be scheduled to perform vulvoscopy if worsening of disease is suspected.

Digital photographs of the vulva will be captured after application of acetic acid to document the clinical findings. If a biopsy or surgical excision is performed, images of the vulva should be collected before and after the procedure. Each site will be instructed on 1) the technique for capturing the proper images using a standard approach, and 2) the process for uploading the images to a secure server.

In the case of multifocal disease, the two lesions that potentially contain the most advanced disease as judged by the Investigator and which is of adequate size to ensure that a visible lesion remains after punch biopsy should be chosen for vulvar biopsy and documented using photography.

Biopsies should not be performed at any visit other than at entry (screening), Week 48, Week 74, or at Week 96 for subjects completing these timepoints prior to or under Amendment 5.0, unless the PI suspects disease progression. All biopsy samples obtained prior to or at the final discharge visit must be sent to the PAC for review. Investigator guidelines for managing the findings of unscheduled biopsies for suspected disease progression are described in Table 12. Consult the Medical Monitor for any planned departures from these guidelines.

Table 12: Guidelines for Managing Findings of Vulvar Biopsies for Suspected Disease Progression

Vulvar Biopsy Results	Action
Vulvar HSIL	May continue study treatment/EP and visits according to protocol schedule of events
Microinvasive or Invasive Carcinoma	Discontinue study treatment/EP and proceed with excisional therapy; continue safety follow-up.

Subject safety is paramount in this study. Therefore, if at any time the Investigator suspects disease progression and the standard of medical care would be to perform an unscheduled biopsy or excision, then his or her medical judgment should prevail over the Schedule of Events on Table 1. Histologic samples and photographic documentation should be obtained for these cases.

6.14 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken within 8 weeks prior to screening biopsy date of eligible subjects must be recorded on the CRF. Actual or estimated start and stop dates must be provided. Medical procedures performed within 8 weeks prior to screening biopsy date of eligible subjects that do not affect subject's eligibility for participation and during the study (including over the counter or herbal), will be recorded on the CRFs. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given per Investigator discretion and recorded in the appropriate sections of the CRF.

6.15 RESTRICTIONS

The following medications and treatments are prohibited:

- Previous treatment with imiquimod for vulvar HSIL within 4 weeks prior to screening
- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, nasal, otic and ophthalmic corticosteroids are allowed)
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study related live vaccine
- Blood thinners/Anticoagulants within 2 weeks of any study treatment

6.15.1 OTHER RESTRICTIONS

Subjects should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the Investigator and/or other study personnel.

Subjects should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to Investigator and/or other study personnel.

Subject should abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to collection of ThinPrep® samples.

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

7.1.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. Throughout the course of the study, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to investigational product(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of study drug).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy (e.g., spontaneous abortion, miscarriage, ectopic pregnancy, fetal demise, still birth, congenital anomaly of fetus/newborn); see Section 7.1.11 for additional information.
- AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study drug period will be recorded as an AE.
- Conditions that lead to a medical or surgical procedure.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed as a result of an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

7.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (even if the hospitalization is only a precautionary measure to allow continued observation). However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly or birth defect;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include 1) allergic bronchospasm requiring intensive treatment in an emergency room or at home, 2) blood dyscrasias or convulsions that do not result in inpatient hospitalization, 3) the development of drug dependency or drug abuse or 4) the development of a malignancy;

7.1.3 CLARIFICATION OF SERIOUS ADVERSE EVENTS

- Death is an outcome of an AE, and not an adverse event in itself.
- The subject may not have been on investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution or are clinically stable. The reporting period for SAEs is described in Section 7.4.2.

7.1.4 EVENT REPORTING FOR DISEASE PROGRESSION OR EXCLUSIONARY HISTOLOGIC FINDINGS POST-STUDY TREATMENT

After starting study treatment, if there is histologic confirmation of progression of HSIL to microinvasive or invasive squamous cell carcinoma, the event must be reported as an SAE. For the finding of carcinoma, subjects should be managed per routine standard of care (i.e. surgical excision), discontinued from study treatment but continue on study without further biopsy. Post-study treatment histologic diagnosis of carcinoma should also be reported as an SAE. In both instances the condition for SAE reporting should be categorized as a medically important event unless another criterion is met.

7.1.5 UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended responses to a medicinal product related to any dose, for which a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e., there is evidence to suggest a causal relationship between the product and the adverse event). An unexpected ADR is one, the nature or severity of which is not consistent with the applicable product information (Investigator's brochure, protocol, and user manual). Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure or protocol would be considered “unexpected”. Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The Sponsor will assess each serious ADR report for expectedness, to determine if it is a serious unexpected suspected adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating Investigators as an expedited report, according to the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor shall notify regulatory authorities and participating Investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected adverse event, the identification of a significant hazard to the subject population, or a major safety finding from a study conducted in animals.

7.1.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of serious adverse event (SAE) that requires expedited reporting on the part of the sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study Investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

7.1.7 ASSESSING SEVERITY (INTENSITY)

Adverse events should be captured once on the CRF at the maximum severity reported. The Investigator will grade laboratory AEs and clinical AEs with respect to the following levels of severity as per Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 for applicable subject populations:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)
- Death (Grade 5)

The Investigator will grade injection site reactions in accordance with September 2007 FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

7.1.8 CASUAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS

A causally related AE is one judged to have a reasonable possibility of a relationship to the administration of the IP and/or the investigational device. An AE may also be assessed as not related to the IP and/or the investigational device. Because the Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting adverse events and judging the relationship between the administration of the IP and device and a subsequent AE. The Investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, available site and non-site laboratory and clinical records, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP and/or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the Investigator as “yes, related” or “no, unrelated” by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or the investigational device;
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable);
- Known association of the event with the IP, EP or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event

7.1.9 ABNORMAL LABORATORY VALUE

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, or SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 7.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the Investigator as clinically significant

7.1.10 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 related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.1.11 PROCEDURES FOR DOCUMENTING PREGNANCY DURING STUDY

Subjects who are pregnant or expect to become pregnant during the course of the study up to 6 months following the last study treatment of investigational product will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further study treatments. A Pregnancy Form will be completed by the site personnel and submitted to the sponsor within 24 hours after learning of the pregnancy. Site personnel will submit the Pregnancy Form to the Sponsor as described in Section 7.4.2.

The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study will continue to be followed for safety assessments without receiving further study treatment. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject. Subjects who are not withdrawn will continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of first study treatment through the follow up visits must be reported. The Investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

7.2 METHODS AND TIMING OF COLLECTION OF SAFETY DATA

Non-serious AEs and SAEs will be collected for each subject from the time when informed consent is obtained through Week 100, or through the final discharge visit for subjects completing the study under Amendment 5.0.

The sources of AEs cover:

1. The subject's response to questions about her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
2. Symptoms spontaneously reported by the subject.
3. Evaluations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
4. Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization).

All AEs will be reported on the appropriate CRF. Any SAE occurring during the course of the study must be reported to the sponsor within 24 hours of awareness.

7.3 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor will be responsible for the overall safety monitoring of the study.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the subject's complaints will be documented.

7.3.1 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100 delivered with CELLECTRA™ 2000 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 of an AESI within 24 hours via method described in Section 7.4.2, to discuss whether further dosing should continue.

7.3.2 STOPPING RULES (CRITERIA FOR PAUSING OF STUDY)

If any of the following situations occur then further enrollment and Study Treatments will be halted until a thorough review has been conducted by the Medical Monitor and PI for the trial, the DSMB, and the IRB/EC (if applicable):

- One third or more subjects experience an AESI verified per protocol definition;
- Any subject experiences an SAE (or potentially life threatening AE), or death verified as related to Study Treatment;
- Three or more subjects experience the same grade 3 or 4 unexpected adverse event, verified per protocol definition and assessed as related to Study Treatment;
- In the event of two identical, unexpected, Grade 4 toxicities, verified per protocol definition and assessed as related to Study Treatment;

Upon conclusion, the sponsor or designee will notify all Investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Guidelines for assessing relatedness are detailed in Section 7.1.8.

7.4 ADVERSE EXPERIENCE REPORTING

To assure the safety of the subjects, information about all AEs (see Section 7.1), whether volunteered by the subject, discovered by Investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

7.4.1 TRIAL REPORTING PERIOD OF ADVERSE EVENTS

All solicited and unsolicited adverse events will be collected throughout the study and recorded in the electronic data capture (EDC) system.

7.4.2 TRIAL REPORTING PERIOD OF SERIOUS ADVERSE EVENTS

The reporting period for SAEs (without regard to causality or relationship) is comprised of the period following the signing of the informed consent form until the end of the study. Each AE will be assessed to determine whether it meets serious criteria. If the AE is considered serious, the Investigator should record this event in the EDC system 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 Ethics Committee according to its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.5 (Suspected Unexpected Serious Adverse Reaction, SUSAR) and 7.1.6 (Unanticipated [serious] adverse device effect) in line with relevant legislation. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the Institutional Review Board (IRB)/Ethics Committee (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 as 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 fax 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 subject identifying information present on SAE supporting documents prior to sending the report to the Sponsor.

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. SAEs must be followed by the Investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

In the event of death, if an autopsy is performed, a copy of the redacted 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.

7.4.3 NOTIFICATION OF SERIOUS ADVERSE EVENTS

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating Investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected and any significant new safety information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. The Sponsor will notify regulatory agencies within the time frame specified by local requirements but no later than 10 working days for UADE, 7 days for a fatal or life-threatening SUSAR and 15 days for all other SUSARS (see Section 7.1.5 and 7.1.6).

7.4.4 REPORTING OF DEVICE RELATED COMPLAINTS

A product complaint (or device deficiency) involves any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device such as malfunction, misuse or use error and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled. All product complaints that meet this definition must be reported to the sponsor within 10 days of discovery. Any product complaint that involves an AE or SAE must be also be reported per Section 7.4.1 and Section 7.4.2.

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.

All complaints must be sent to ClinicalComplaint@inovio.com. Additional instructions on complaint reporting to be provided separately.

7.5 TRIAL DISCONTINUATION

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all non-source documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

The study may be discontinued at any time by an IRB, Inovio Pharmaceuticals Inc., the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

8. STATISTICAL ANALYSIS PLAN

8.1 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a two-arm, multi-center, open-label randomized clinical trial of VGX-3100 and VGX-3100 with imiquimod, in subjects with a histologic diagnosis vulvar HSIL and confirmed vulvar infection with HPV types 16 and/or 18. The study's primary endpoint is binary: regression of vulvar HSIL and viral clearance of HPV-16 and/or HPV-18 from vulvar tissue based on tissue collected at Week 48. The primary hypothesis is that each of the treatment arms will result in regression of HSIL and clearance. Secondary efficacy analyses pertain to regression, clearance of HPV-16 and/or HPV-18 infection, regression to normal, 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, and anatomic extent, and clearance outside of the vulva. Other exploratory analyses pertain to humoral, cellular, and tissue immunological measures and patient-reported outcomes.

8.2 RANDOMIZATION AND BLINDING

Subjects will be randomized two to one, VGX-3100 alone: VGX-3100 in combination with topical imiquimod. Subjects will be randomized in a stratified manner according to (a) recurrent disease at screening (0 vs. 1 or more recurrences), (b) multifocal disease (1 vs. 2 or more lesions at screening), (c) Body Mass Index (BMI) category (≤25 vs. >25 kg/m^2) on Day 0, and (d) age category (<45 years vs. ≥45 years) on Day 0. There are no requirements for the number of subjects in each stratum. The study is open-label.

The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

8.3 SAMPLE SIZE/POWER

A sample of 36 subjects will be randomized to receive either 6 mg VGX-3100 or 6 mg VGX-3100 plus imiquimod, IM followed by EP in a 2:1 ratio. This sample size provides 80% power to declare each study group superior to historical control with a one-sided

0.025 type 1 error level for each hypothesis, assuming the true proportion of subjects who achieve the primary endpoint is 20% and 28% for the respective treatment arms and 2% for the historical control, and that 90% are evaluable at Week 48 from randomization.

The Version 3.0 protocol amendment halts enrollment of the VGX-3100 with topical imiquimod study group. All subjects who have already been enrolled into the VGX-3100 with imiquimod study group will continue with all study visits per protocol, but no further participants will be enrolled into this group.

8.4 ANALYSES POPULATIONS

Analysis populations will include:

- The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be primary for the analysis of efficacy in this study.
- The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.
- The safety analysis set includes all subjects who receive at least one does of Study Treatment. Subjects will be analyzed as to the treatment they received.

8.5 SUBJECT DISPOSITION

Disposition will be summarized by treatment for all randomized subjects and will include the number and percentage randomized, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

8.6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the mITT population. Prior and concomitant medications will also be summarized with percentages in this fashion.

8.7 MEDICAL HISTORY

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the mITT population.

8.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are considered those medications taken prior to the first dose of study drug (i.e., Day 0). Concomitant medications are those used on or after Day 0. Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the mITT population.

8.9 EFFICACY ANALYSIS

The true treatment effect on the primary endpoint is p, where p denotes the true population probability of the primary endpoint for each arm. The primary hypothesis of superiority is:

H0: $p \leq 0.02$ *vs*. H1: $p > 0.02$, for each treatment study group separately.

A p-value for these hypothesis tests and corresponding 95% confidence intervals will be computed based on the exact method of Clopper-Pearson. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds 0.02.

The secondary efficacy binary endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values. All of the efficacy binary endpoints will be analyzed in two ways: a) based on qualifying and new lesions, and b) based on all lesions. Also, the Week 74 binary endpoint will be analyzed overall, and according to four or five doses received, and the Week 96 binary endpoint will be analyzed overall, and according to four, five, or six doses received.

For the analyses, the efficacy time frame is defined by any time starting from 14 days prior to the -specified visit week.

The anatomic extent endpoint will be analyzed by calculating the mean percent change and associated 95% t-distribution based confidence interval. The percentage of subjects with no clinically significant lesion resolution (reduction in lesion size of 25% or less), partial lesion resolution (26-99% reduction), and complete reduction (100% reduction) will be summarized with point estimates and associated exact Clopper-Pearson 95% confidence intervals.

An exploratory analysis will examine clearance outside of the vulva. This will be analyzed in the same manner as vulvar clearance.

An exploratory analysis will examine the relationship between the primary efficacy endpoint and a) miRNA results, b) vulvoscopy results, and c) HPV results. Relationships will be examined with contingency tables and/or logistic regression models which model the primary endpoint versus these results and treatment group as regressor variables.

8.10 IMMUNOGENICITY ANALYSIS

Post-baseline cellular and humoral response magnitude will be summarized with medians and associated non-parametric 95% CIs. Post-baseline tissue response magnitude will be summarized with means and associated t-distribution based 95% CIs.

Valid samples for statistical analysis purposes will be those collected within 7 or 14 days of the specified time points (see Table 1). Baseline is defined as the last measurement prior to the first treatment administration.

8.11 SAFETY ANALYSES

All AEs will be summarized among the safety population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 14 days of any dose. For this summary, the frequency of preferred term events will be summarized with percentages and exact Clopper-Pearson 95% confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

Any AEs with a missing or partial onset date will be included in the overall AEs, but not be included within specified day-range summaries. AE duration will be calculated as (Stop Date – Start Date) + 1.

Measurements for vital signs as well as changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and treatment arm, for the mITT population. Baseline is defined as the last measurement prior to the first treatment administration.

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment study group and by body system, for the mITT population.

8.12 PATIENT REPORTED OUTCOMES

As an exploratory endpoint, patient reported outcomes will be summarized with medians or proportions of subjects with endpoints and associated non-parametric or exact Clopper-Pearson 95% CIs, for continuous responses and binary responses, respectively.

8.13 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

8.14 INTERIM ANALYSES

No formal interim analyses will be performed for this study.

9. ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The Investigator and Sponsor are responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

9.2 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE (IRB/EC)

The Investigator will undertake the study after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/EC and a copy of this approval has been received by the sponsor.

Investigator responsibilities relevant to the IRB include the following:

- During the conduct of the study, submit progress reports to the IRB/EC as required.
- Notify the Sponsor immediately of any SAEs or serious unanticipated adverse device effects.
- If Sponsor notifies you about any reportable safety events notify the IRB immediately.
- As required, obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
- Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the Investigator at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of study-related information that includes all correspondence with the IRB;
- Notify IRB when study is completed (i.e. after the last study visit of the final study subject);
- After study completion provide the IRB with a final report on the study.

9.3 OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The Investigator and Sponsor are responsible for ensuring that the clinical study is reviewed and approved according to local and applicable global regulations (e.g., NIH Office of Biotechnology Activities) governing research that involves recombinant or synthetic nucleic acid molecules.

9.4 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to Screening into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

9.5 COMPLIANCE WITH IRB/EC REQUIREMENTS

This study is to be conducted in accordance with applicable IRB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/EC prior to initiating the study and re-approval or review at least annually. Sponsor is to be notified

immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/EC correspondence with the Investigator must be provided to Sponsor.

9.6 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

9.7 COMPLIANCE WITH ELECTRONIC RECORDS/SIGNATURES REGULATIONS (21CFR PART 11)

When applicable, this study is to be conducted in compliance with the regulations on electronic records and electronic signature.

9.8 COMPLIANCE WITH PROTOCOL

Subjects will be asked to complete a participant diary and, for subjects in the imiquimod study group, a dosing log during their study participation. Subjects will be provided with Investigator emergency contact information and advised to report all adverse events. While every effort should be made to avoid protocol deviations, should a deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

9.9 CHANGES TO THE PROTOCOL

The Investigator should not implement any deviation from or changes to the protocol without approval by the Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

10. DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study sponsor, Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA)).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

The rights of the research subject to revoke their authorization for use of their PHI.

10.2 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial.

A medical history must be present in the source documents. A medication history must be present in the source documents. All prescription and nonprescription medications taken within l week prior to entry must be recorded on the CRF. Actual or estimated start and stop dates must be provided.

10.3 RECORDS RETENTION

Upon request of the monitor, auditor, IRB/EC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the Investigator/institution as to when these documents are no longer needed to be retained.

10.4 SAFETY AND QUALITY MONITORING

10.4.1 DATA & SAFETY MONITORING BOARD

A Data & Safety Monitoring Board (DSMB) will be established to protect the research subjects through independent analysis of emerging data from the trial. The DSMB will meet quarterly or as data are available to review safety data and regression/clearance results. If there are no new safety data or regression/clearance results to review for a quarterly scheduled meeting the DSMB will be notified and the meeting may be cancelled; Ad hoc meetings may be scheduled to review new data as applicable. The DSMB will be charged with advising the Sponsor if there appears to be a safety issue. No formal interim analysis will be performed. The DSMB Chair, upon consultation with the other voting members of the DSMB, has the authority to recommend suspension or stopping the study and to request a full DSMB review and ad hoc statistical analyses. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Inovio.

10.4.2 PATHOLOGY ADJUDICATION COMMITTEE

All vulvar 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 up to four pathologists. Each specimen will be read by two pathologists independently in a masked fashion. The responsibilities and membership structure of the PAC is outlined in the PAC Charter, including the reporting of results.

10.4.3 CLINICAL MONITORING

Clinical Monitoring of the trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the study.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
  - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies
  - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB
  - Throughout the study, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOAC).
  - Assure that the study facilities continue to be acceptable

- Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate
- Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements

11. PUBLICATION POLICY

Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to The Sponsor 60 days prior to submission for publication. The Sponsor shall have thirty (30) days after receipt of the copies to object to the proposed presentation or publication because there is patentable subject matter that needs protection. In the event that The Sponsor makes such objection, the researcher(s) shall refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable subject matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

12. LIST OF ABBREVIATIONS

AE	Adverse Event
ACOG	American College of Obstetricians and Gynecologists
AIN	Anal Intraepithelial Neoplasia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CPK	Creatine Phosphokinase
CRF	Case Report Forms
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSMB	Data & Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation with Cellectra™ 2000
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
HSIL	High grade squamous intraepithelial lesion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IXRS	Interactive Response Technology
LAST	Lower Anogenital Squamous Terminology
mITT	Modified Intent to Treat
NIH	National Institutes of Health
OP	Oropharyngeal
Principal Investigator	Lead Investigator for overall study activities
Investigator	Lead Investigator for individual site(s)
PAC	Pathology Adjudication Committee
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Participant Diary
PE	Physical exam

PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SID	Subject Identification
SOC	System Organ Class
TNF	Tumor Necrosis Factor
UADE	Unanticipated Adverse Device Effect
VAIN	Vaginal Intraepithelial Neoplasia
WOCBP	Women of Childbearing Potential
WOMAN-PRO	WOMen with vulvAr Neoplasia PRO

13. REFERENCES

1. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. . Human Papillomavirus and Related Diseases in USA., ICO Information Centre on HPV and Cancer (HPV Information Centre), Summary Report 30 June 2017. 2017.

2. Bruni L B-RL, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. Human Papillomavirus and Related Diseases in Europe. ICO Information Centre on HPV and Cancer (HPV Information Centre) Summary Report 30 June 2017. 2017.

3. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW*, et al.* US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst* 2015,**107**:djv086.

4. National Cancer Institute S, Epidemiology, and End Results Program (SEER) Stat Fact Sheets: Vulvar Cancer. 2016.

5. Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjose S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. *Infect Agent Cancer* 2017,**12**:19.

6. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. *Bethesda, MD* 2015.

7. Salom EM PM. Recurrent vulvar cancer. *Curr Treat Options Oncol* 2002,**3**:143-153.

8. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J*, et al.* Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015,**386**:2078-2088.

9. Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J*, et al.* Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005,**50**:807-810.

10. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD*, et al.* The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis* 2012,**16**:205-242.

11. Inovio Pharmaceuticals. Unpublished assessment. 2015.

12. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. *Obstet Gynecol* 2005,**106**:1319-1326.

13. van Seters M vBM, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005,**97**:645-651.

14. Inovio Pharmaceuticals. Personal communications from consultants to Inovio. 2015.

15. ACOG. Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. *Obstet Gynecol* 2011,**118**:1192-1194.

16. Frega A, Sopracordevole F, Scirpa P, Biamonti A, Lorenzon L, Scarani S*, et al.* The re-infection rate of high-risk HPV and the recurrence rate of vulvar intraepithelial neoplasia (VIN) usual type after surgical treatment. *Med Sci Monit* 2011,**17**:CR532-535.

17. ACOG. Committee Opinion No. 675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol.* 2016,**128**:e178-182.

18. Inovio Pharmaceuticals. VGX-3100 Assessment. Unpublished Market Research. 2014.

19. Inovio Pharmaceuticals. Vulvar Intraepithelia Neoplasia Patient Journey. Unpublished Market Research. 2016.

20. Senn B, Eicher M, Mueller MD, Hornung R, Fink D, Baessler K*, et al.* A patient-reported outcome measure to identify occurrence and distress of post-surgery symptoms of WOMen with vulvAr Neoplasia (WOMAN-PRO) - a cross sectional study. *Gynecol Oncol* 2013,**129**:234-240.

21. Likes WM SC, Tillmanns T, Pruett J. Pilot study of sexual function and quality of life after excision for vulvar intraepithelial neoplasia. *J Reprod Med* 2007,**52**:23-27.

22. Petrosky E, Bocchini JA, Jr., Hariri S, Chesson H, Curtis CR, Saraiya M*, et al.* Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 2015,**64**:300-304.

23. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007,**356**:1915-1927.

24. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. *J Clin Pathol* 2014,**67**:290-294.

25. Aihara H, Miyazaki J. Gene transfer into muscle by electroporation in vivo. *Nat.Biotechnol.* 1998,**16**:867-870.

26. Gehl J, Mir LM. Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization. *Biochemical and Biophysical Research Communications* 1999,**261**:377-380.

27. Sardesai NY, Weiner DB. Electroporation delivery of DNA vaccines: prospects for success. *Curr.Opin.Immunol.* 2011,**23**:421-429.

28. van Drunen Littel-van den H, Hannaman D. Electroporation for DNA immunization: clinical application. *Expert.Rev.Vaccines.* 2010,**9**:503-517.

29. Bodles-Brakhop AM, Heller R, Draghia-Akli R. Electroporation for the Delivery of DNA-based Vaccines and Immunotherapeutics: Current Clinical Developments. *Mol Ther.* 2009.

30. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC*, et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012,**4**:155ra138.

31. Senn B. Creating and Validating a Patient-Reported Outcome Instrument for Women with Vulvar Neoplasia after Surgical-Treatment - A Mixed-Methods Project, Institute of Nursing Science (INS) University of Basel, University Hospital Berne, Switzerland. 2012.

32. Senn B, Mueller MD, Hasenburg A, Blankenstein T, Kammermann B, Hartmann A*, et al.* Development of a postsurgical patient-reported outcome instrument for women with vulvar neoplasia. *Oncol Nurs Forum* 2012,**39**:E489-498.

33. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) CfBEaRC, Center for Devices and Radiological Health (CDRH). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. 2009.

34. Aldara (imiquimod) Cream. Highlights of Prescribing Information. 2010.

35. Perrigo. Imiquimod Cream, 5%. Highlights of Prescribing Information. 1997.

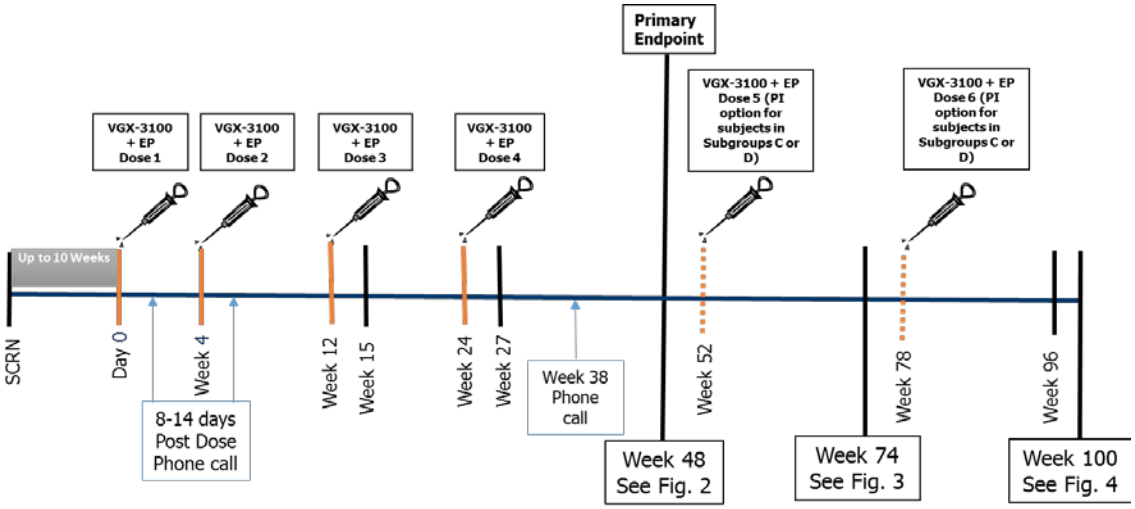
36. Maruish M. User's manual for the SF-36v2 Health Survey (3rd ed.). 2011.

37. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L*, et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013,**22**:1717-1727.

38. EuroQol. EuroQol-- a new facility for the measurement of health-related quality of life. *Health Policy* 1990,**16**:199-208.

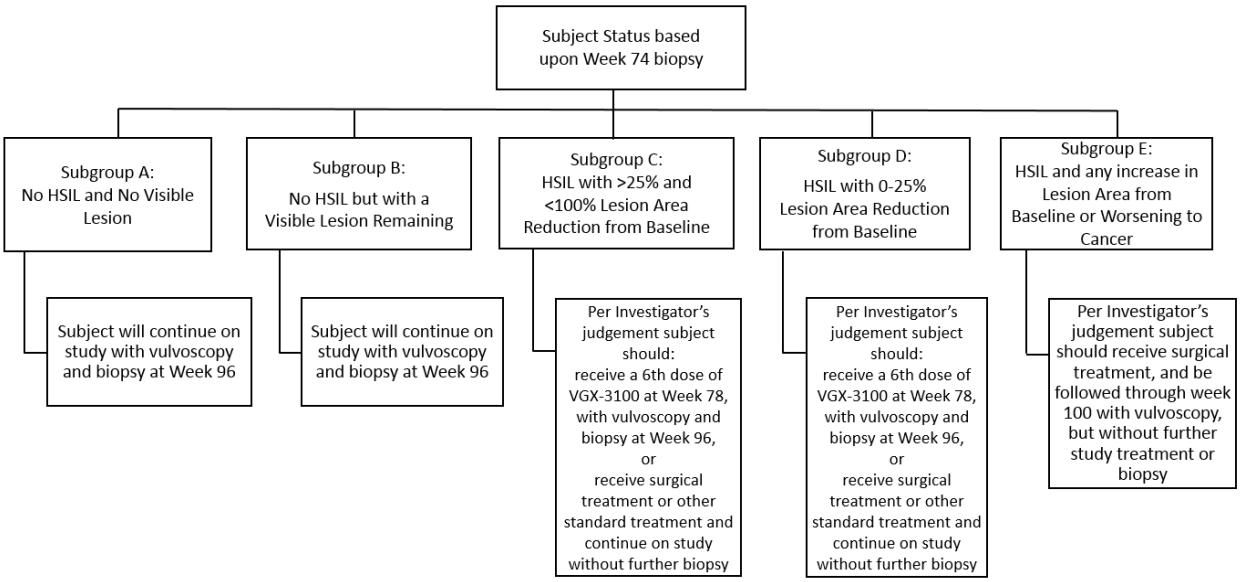
14. APPENDICES

APPENDIX A: FIGURE 1. STUDY VISIT SCHEDULE, ORIGINAL STUDY DESIGN



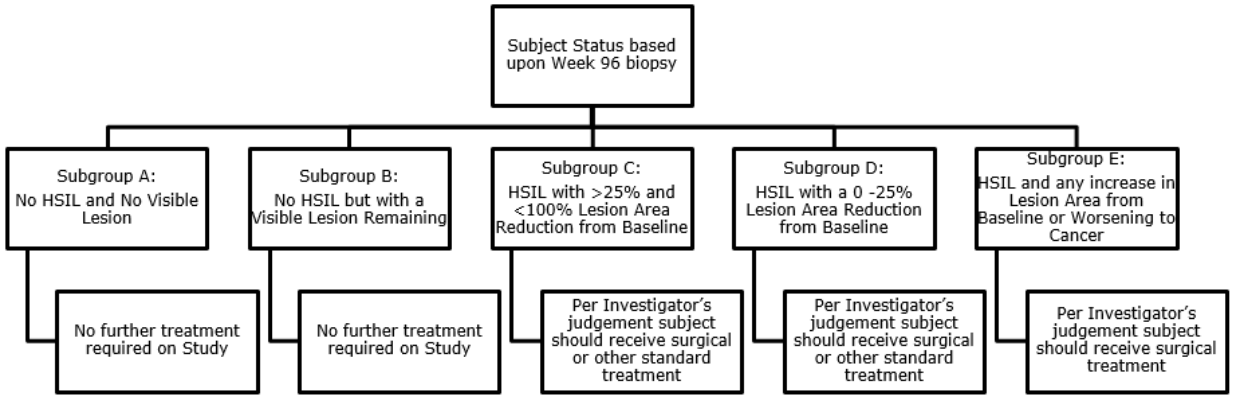
The first dose is administered on Day 0, the second at Week 4, the third at Week 12, and the fourth dose at Week 24. Subjects with no HSIL at Week 48 (Subgroups A and B) will receive 4 doses. Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a fifth dose of VGX-3100 administered IM with EP at Week 52 per the judgment of the Investigator. Subjects with HSIL at Week 74, who have a reduction in lesion size or no increase in lesion size from baseline (Subgroups C or D), may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator. Subjects in Subgroup E may receive surgical treatment per the judgment of the Investigator. All subjects are scheduled to be followed to Week 100.

APPENDIX B: FIGURE 3. DECISION PROCESS AT WEEK 78, ORIGINAL STUDY DESIGN



The decision process following results of the Week 74 biopsy are described in Figure 3 and are as follows: At Week 74, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If after evaluation of biopsy tissue by the PAC there is no evidence of HSIL (Subgroups A or B), the subject will continue to Week 96 for vulvoscopy, and biopsy of the same area from the region of potentially most advanced disease based upon the judgment of the Investigator. If HSIL remains but there is a reduction in lesion size or no change in lesion size from baseline (Subgroups C or D), the Investigator has the option to give the subject a 6th dose of VGX-3100 at Week 78, and the subject will continue on study with vulvoscopy and biopsy at Week 96. Alternatively, the Investigator may choose to treat the subject with surgical or standard treatment, and the subject will continue on study without further biopsy.

APPENDIX C: FIGURE 4. EVALUATION PROCESS AT WEEK 100, ORIGINAL STUDY DESIGN



The decision process following results of the Week 96 biopsy are described in Figure 4 and as follows:

At Week 96, the subject will undergo repeat vulvar punch biopsy/biopsies of the same lesion as study start from the region of potentially most advanced disease based upon the judgment of the Investigator (see Table 2). If there is no vulvar HSIL (Subgroups A or B), no further procedures are required. If after evaluation of biopsy tissue by the PAC there is vulvar HSIL (Subgroups C or D), or worsening disease (Subgroup E), the subject will receive surgical or other standard treatment.