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:	Statistical Analysis Plan Final Version 2.0: 22 March 2021

STATISTICAL ANALYSIS PLAN

Protocol 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

Protocol Number:	HPV-201
Protocol Version and Date:	Version 5.0: 19 December 2019 Version 4.0: 13 September 2019 Version 3.0: 26 March 2019 Version 2.0: 20 November 2017 Original 1.0: 13 January 2017
Name of Test Drug:	VGX-3100
Phase:	Phase 2
Methodology:	Prospective, Randomized, Open-label
Sponsor:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462 Tel: (267) 440-4200 Fax: (267) 440-4242
Sponsor Representative:	[redacted] PhD [redacted]
Analysis Plan Date:	22 March 2021
Analysis Plan Version:	Final Version 2.0

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Inovio Pharmaceuticals, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Inovio Pharmaceuticals, Inc. is expressly prohibited.

APPROVAL SIGNATURE PAGE

Protocol 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
Sponsor:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462
Protocol Number	HPV-201
Document Date / Version:	22 March 2021 / Final Version 2.0
Veristat ™, LLC. Author:	[redacted] MS

Approval Signature	Job Title
	[redacted]

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory: [redacted] PhD
[redacted]

Approval Signature	Job Title
	[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomic therapeutic class
BMI	Body mass index
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ELISpot	Enzyme linked immunosorbent spot-forming
EP	Electroporation
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HPV-16/18	HPV-16 and/or HPV-18
HSIL	High grade squamous intraepithelial lesion
ICH	International Conference on Harmonisation
IFN-γ	Interferon gamma
IM	Intramuscular
IRB	Institutional Review Board
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MiRNA	MicroRNA
mITT	Modified intention-to-treat
PBMC	Peripheral blood mononuclear cells
PCS	Physical Component Summary
PP	Per-protocol
PRO	Patient reported outcomes
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SD	Standard deviation
SI	International System of Units
SLR	Single-lens reflex
SOC	System organ class
TEAE	Treatment-emergent adverse event
VIN	Vulvar intraepithelial neoplasia
WOMAN-PRO	WOMen with vulvAr Neoplasia PRO

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Human papillomaviruses (HPV) are double-stranded deoxyribonucleic acid (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-16/18 is involved in about 83% of HPV-associated vulvar high grade squamous intraepithelial lesion (HSIL) cases in the U.S. [1] and about 72% in Europe [2]. Persistent infection with 1 or more oncogenic (high-risk) HPV genotypes can lead to the development of precancerous, histologic HSIL. 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 [3] and about 9,776 new cases in 2015 in Europe [4]. Vulvar cancers consist largely of squamous cell carcinomas and accounts for approximately 5% of all female genital malignancies [5].

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 1 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].

Vulvar HSIL remains a significantly under met 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.

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. 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 [7, 8].

A 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 intramuscularly (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 [9].

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.

1.1.2. Statistical Analysis Plan Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.3. Study Objectives

1.1.3.1. Primary Objective

The primary objective is to determine the efficacy of 4 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.

1.1.3.2. Secondary Objectives

The secondary objectives include the following:

- To evaluate the safety and tolerability of VGX-3100 delivered IM followed by EP with CELLECTRA™ 2000, alone or in combination with imiquimod
- To determine the efficacy of 4 doses of VGX-3100, alone or in combination with imiquimod, as measured by histologic regression of vulvar HSIL
- To determine the efficacy of 4 doses of VGX-3100, alone or in combination with imiquimod, as measured by virologic clearance of HPV-16/18 in vulvar tissue
- To determine the efficacy of 4 doses of VGX-3100, alone or in combination with imiquimod, as measured by histologic regression of vulvar HSIL to normal tissue
- To determine the efficacy of 4 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
- To determine the efficacy of VGX-3100, alone or in combination with imiquimod, as measured by reduction in the surface area of the qualifying vulvar lesion(s)
- To describe the cellular immune response of VGX-3100 administered alone or in combination with imiquimod, post dose 4
- To 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

1.1.3.3. Exploratory Objectives

The exploratory objectives include the following:

- To 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 vulvar lesion(s), in subjects without a complete lesion resolution at Week 48
- To describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by histologic regression of vulvar HSIL
- To describe the long term efficacy of VGX-3100, alone or in combination with prior imiquimod, as measured by virologic clearance of HPV-16/18
- To evaluate tissue immune responses to VGX-3100, and VGX-3100 with imiquimod, as measured in vulvar tissue samples
- To describe virologic clearance of HPV-16/18 from non-vulvar anatomic locations
- To describe association of microRNA (miRNA) profile, previous vulvoscopy, and HPV testing results with Week 48 histologic regression
- To describe patient reported outcomes (PRO) for subjects treated with VGX-3100 and VGX-3100 with imiquimod
- To 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
- To 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

1.2. Study Design

1.2.1. Synopsis of 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.

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 2 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 (CRF). 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.

All eligible subjects who consent to participate in the study will receive at least 4 doses of 6 mg of VGX-3100 administered by IM injection followed by EP. 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 3 times per week for 20 weeks (inclusive of administration in the evening of VGX-3100 dosing).

Subjects will be placed into the following subgroups depending on status of biopsies performed at Week 48, Week 74, and Week 96:

- Subgroup A: Subjects having no HSIL and no visible lesions
- Subgroup B: Subjects having no HSIL but with a visible lesion
- Subgroup C: Subjects having HSIL with >25% and <100% lesion area reduction from baseline
- Subgroup D: Subjects having HSIL with 0-25% lesion area reduction from baseline
- Subgroup E: Subjects having HSIL and any increase in lesion area from baseline or worsening to cancer

Subjects in Subgroups C and D may receive a fifth and possibly a sixth dose at Week 52 and Week 78, respectively.

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 2 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 up to100 weeks for the treatment and follow-up periods. The study duration is reduced to 78 weeks for subjects that have not already completed the Week 78 visit.

1.2.2. Randomization Methodology

Subjects are randomized by Y-Prime, Inc. to VGX-3100 alone or VGX-3100 in combination with imiquimod in a 2:1 ratio using a central randomization algorithm. Randomization will be done 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/m2), and (d) age category (<45 years vs. ≥45 years).

1.2.3. Stopping Rules and Unblinding

No blinding will be done for this study as the study is open-label.

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 Principal Investigator for the trial, the Data Safety Monitoring Board (DSMB), and the Institutional Review Board (IRB) / Ethics Committee (EC) (if applicable):

- One-third or more subjects experience an adverse event of special interest (AESI) verified per protocol definition;
- Any subject experiences a serious adverse event (SAE) (or potentially life-threatening adverse event [AE]) or death verified as related to study treatment;

- Three or more subjects experience the same Grade 3 or 4 unexpected AE, verified per protocol definition and assessed as related to study treatment;
- In the event of 2 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.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments

Tests and Observations	Screening (-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 [1]	X	X		X		X		X	X		X	X	X	X	X	X
Vital signs	X[2]	X		X		X		X	X		X	X	X	X	X	X
Screening safety (12 lead ECG, labs) [3]	X															
Pregnancy Testing [4]	X	X		X		X		X	X		X	X	X	X	X	X
HIV Ab by ELISA	X															
Blood immunologic samples	X[5]	X[5]					X[5]		X[6]		X[5]		X[5]		X[5]	
OP rinse, vaginal, and intra-anal swabs		X							X		X		X		X	
Vulvar swabs		X		X		X			X		X		X		X	

Tests and Observations	**Screening (-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)**
Cervical colposcopy[7]		X													X	
Cervical cytology, ThinPrep® [8]		X				X					X				X	
Vulvoscopy [9]	X	X		X		X			X		X		X		X	
Vulvar lesion standardized photography [10]	X	X		X		X			X		X		X		X	
Biopsy [11]	X										X		X		X	
Vulvar HPV genotyping [12]	X										X		X		X	
Inject VGX-3100 +EP [12, 13]		X		X		X		X				X[13]		X[13]		
Post treatment reaction assessment		X		X		X		X				X		X		
Dispense imiquimod + distribute imiquimod dosing log [14]		X		X		X										
Review imiquimod dosing log and usage				X		X		X								
Distribute Participant Diary (PD)		X		X		X		X				X		X		
Review PD [15]			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) [16]		X	X	X	X	X	X	X	X		X	X	X		X	X

* Subjects completing the study before Week 100 will have the final socio-behavioral assessment done at their final discharge visit. This may be obtained by phone.

[1] 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.

[2] 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.

[3] 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.

[4] Negative spot urine pregnancy test is required at screening and prior to each study treatment, vulvoscopy and biopsy/surgical excision.

[5] 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.

[6] At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 27.

[7] 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.

[8] HPV genotyping and Pap smears are performed on the same ThinPrep® cervical specimen.

[9] 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.

[10] 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.

[11] 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.

[12] HPV genotyping is performed on vulvar tissue specimen using a PCR based assay.

[13] 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 6^{th} dose.

[14] Subjects will take home imiquimod plus an imiquimod dosing log to document their use of imiquimod. Administration of imiquimod begins on Day 0.

[15] 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.

[16] PRO measures (SF-36v2™, EQ-5D-5L, WOMAN-PRO) plus 2 additional questions will be assessed as described in protocol Section 6.8.

1.2.5. Efficacy, Immunology, and Safety Parameters

1.2.5.1. Efficacy Parameters

The primary efficacy endpoint is the combined response outcome of histopathologic regression of vulvar HSIL and virologic clearance of HPV-16/18 in vulvar tissue at Week 48.

The secondary efficacy endpoints include the following:

- Histopathological regression is defined as no histologic evidence of vulvar HSIL at Week 48.
- Virologic clearance is defined as no evidence of HPV-16/18 at Week 48 in vulvar tissue samples.
- Proportion of subjects with no histologic evidence of vulvar HSIL or no evidence of HPV-16/18 at Week 48 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).
- 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.
- Proportion of subjects with no progression of vulvar HSIL to vulvar cancer from baseline to Week 48 visit.
- Percent reduction in the cumulative surface area of qualifying 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. 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),
    - Complete lesion resolution (no visible lesion).

Exploratory efficacy endpoints include the following:

- 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. 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).
- 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 VGX3100 and at Week 96 for subjects who receive 6 doses of VGX-3100.
- Virologic clearance in vulvar tissue samples at Week 74 and/or Week 96 compared to baseline.
- Virologic clearance from non-vulvar anatomic locations without surgical intervention at Week 48 compared to baseline.

- The relationship of microRNA (miRNA) profile (Day 0, Week 15, and Week 48), previous vulvoscopy, and HPV testing results (vulvar swab and vulvar tissue) with Week 48 histologic regression of vulvar HSIL.
- Proportion of subjects at Week 74 and 96 with no histologic evidence of vulvar HSIL or no evidence of HPV-16/18 in vulvar tissue samples (i.e. collected via biopsy or excisional treatment).

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) Clinical Trial Version 2.0, and 2 additional PRO questions assessing quality of life after surgery or biopsy. The PRO instruments are described below.

- WOMAN-PRO - is a 31 item self-completed patient reported outcome measure designed to assess both physical and psychosocial impacts of VIN.
- SF-36v2 – generically measures functional health and well-being, for physical and mental health. The questionnaire consists of 36 items covering 8 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).
- EQ-5D-5L – generically measures activities and general health status and consists of 6 items covering 6 domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status).

1.2.5.2. Immunology Parameters

The secondary immunology endpoint is the Flow Cytometry response magnitudes at baseline and Week 27 visits.

Exploratory immunology endpoints include the following:

- Assessment of pro-inflammatory and immunosuppressive elements in vulvar tissue, which may include visualization of PD-L1, Granulysin, perforin, CD137, CD103, and possibly other relevant markers.
- Levels of serum anti-HPV-16 and antiHPV-18 antibody concentrations at baseline, Weeks 15, 27, 48, 74, and 96 visits.
- Interferon-γ ELISpot response magnitudes at baseline and Weeks 15, 27, 48, 74 and 96 visits.
- Immunohistochemistry biomarker results including but not limited to, CD8+ and FoxP3+ infiltrating cells as well as assessment of cell death via Cleaved Caspase 3 assessment.

1.2.5.3. Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs, and monitoring of AEs, injection site reactions, pain, and concomitant medications.

Secondary safety endpoints include the following:

- Local and systemic events for 7 days following each dose as noted in the Participant Diary
- All adverse events including SAEs, AESIs, SUSARs, UADEs, and other unexpected AEs for the duration of the study (through Week 100 visit)

Treatment-emergent adverse events (TEAEs) are collected throughout study. All TEAEs that occur within 7, 14, or 28 days following each injection will be summarized separately.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Modified Intention-to-Treat (mITT) Population: All subjects who receive at least 1 dose of VGX-3100 + EP and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized.
- Per-protocol (PP) Population: All subjects who receive at least 4 doses of VGX-3100 + EP, have no protocol violations, and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to locking of the study database.
- Safety Population: All subjects who receive at least 1 dose of VGX-3100 (with or without EP). Subjects will be analyzed as to the treatment they received.

The mITT population is the primary population for the analysis of efficacy parameters. The PP population will be considered supportive of the corresponding mITT population for the analysis of efficacy. The Safety population is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

At the discretion of the Sponsor, protocol violations, as determined by a review of the data prior to locking of the study database and the conduct of statistical analyses, will result in the removal of a subject's data from the PP population. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol violation which warrant exclusion from the PP population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

Relevant Output

Listing 16.2.2.2 Protocol Violations

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The study will enroll 36 subjects 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 1-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% of subjects in each treatment group are evaluable at Week 48 from randomization.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication (Day 0) which is designated as Rel Day 1. The preceding day is Rel Day -1, the day before that is Rel Day -2, etc. There is no Rel Day 0.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, immunogenicity, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Summarizations will be presented by treatment grouping and overall as applicable.

Formal statistical hypothesis testing will be performed on the primary endpoint for each treatment group compared to historical control separately at a 1-sided, 0.025 level of significance. Summary statistics will be presented, as well as 2-sided 95% confidence intervals (CIs) on selected efficacy and safety parameters, as described in the sections below.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software Version 9.3 or higher, unless otherwise noted. Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA), starting with Version 20.0.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug.

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

No adjustments for multiple testing will be implemented, as 2 one-sided tests will each utilize a type I error rate of 2.5% on testing the primary hypothesis.

3.8. Subpopulations

Certain subgroups will be analyzed separately at additional time points for effectiveness of additional doses and/or surgical treatments.

- Subgroups A and B – Subjects with no HSIL at Week 48 will receive 4 doses.
- Subgroups C and D – Subjects with HSIL at Week 48, who have a reduction in lesion size or no increase in lesion size from baseline, 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 may receive a sixth dose of VGX-3100 administered IM with EP at Week 78 per the judgment of the Investigator.
- Subgroup E – Subjects may receive surgical treatment per the judgment of the Investigator.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

When tabulating AE data, partial dates will be handled as follows in order to determine treatment emergence. If any of the day, month, or year is missing, the onset date will be set to the earliest date that is consistent with any non-missing date information, unless the non-missing date information is the same as study treatment start. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of start of treatment. A completely missing onset date will be coded as the day of start of treatment.

A prior medication is defined as any medication that has a stop date before the start of the trial (prior to Dose #1 on Day 0). A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug. For prior and concomitant medications, partial start dates will not be imputed, as stop dates determine prior versus concomitant. Partial stop dates will be assumed to be the latest possible date consistent with the partial date.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

The efficacy time windows for histologic regression and virologic clearance are defined by samples obtained any time starting from 14 days prior to the protocol-specified target date of visit.

3.12. Interim Analyses

For reasons of futility (early observational evidence of poor efficacy of VGX-3100), the study has the potential to be stopped by the DSMB at any time. However, no formal interim analyses are planned, and the study is not designed to be stopped early based on evidence of efficacy.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated by treatment group and overall, and will include the number screened, the number of screen failures, the number randomized (in total and by stratum), the number treated by the highest number of doses received, the number in each subject population for analysis, the number that completed all study treatments and follow-up visit, the number who withdrew prior to completing the study treatment, the number who withdrew prior to completing all follow-up visits, and reason(s) for withdrawal. Reasons for not participating in study will also be summarized.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented. Consent and randomization, inclusion/exclusion criteria, and study populations will also be provided in listings.

Relevant Output

Table 14.1.1.1	Subject Enrollment and Disposition
Table 14.1.1.2	Summary of Primary Reasons for Not Participating in Study
Listing 16.2.1.1	Study Completion Status
Listing 16.2.1.2	Consent and Randomization Information
Listing 16.2.2.1	Inclusion/Exclusion Criteria and Eligibility
Listing 16.2.3.1	Study Populations
Listing 16.2.3.2	Randomized Subjects Who Were Never Vaccinated
Listing 16.2.3.3	Subject Status Subgroups

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by treatment group and overall. Age, height, weight, and BMI will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). The number and percentage of subjects in each randomization stratum, ethnicity category, race category, and country also will be presented. Results at screening for VIN category, HPV type, years of education, and type of insurance will also be presented.

Abnormal medical history will be summarized by term as collected on the electronic CRF. Prior vulvar disease, HPV diagnoses, and reproductive history will be presented in data listings as well as tobacco history and alcohol use.

No formal statistical comparisons between groups will be performed for demographics, baseline data, or medical history data. Data for each subject will also be provided in data listings.

Relevant Output

Table 14.1.2.1A	Demographics and Baseline Characteristics (mITT/Safety Population)
Listing 16.2.4.1	Demographics and Baseline Disease Characteristics
Listing 16.2.4.2	Abnormal Medical History
Listing 16.2.4.3	Prior Vulvar Disease and HPV Diagnoses
Listing 16.2.4.4	Reproductive System History
Listing 16.2.4.5	Alcohol, Tobacco, and Recreational Drug Use

4.3. Efficacy Evaluation

Efficacy analyses will be conducted using the mITT population. Supportive analyses of efficacy will be based on the PP population.

4.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the combined outcome of histologic regression of vulvar HSIL and virologic clearance of HPV-16/18 at Week 48. Histologic regression is defined as no histologic evidence of vulvar HSIL (normal tissue or vulvar LSIL (VIN 1) or condyloma) at Week 48. Virologic clearance is defined as clearance of HPV 16 or 18 at Week 48. A subject achieves the primary outcome (i.e., is a "responder") if histologic regression and virologic clearance is observed at Week 48 and the subject did not receive any non-study related treatment for vulvar HSIL. A subject is a non-responder if there is histologic evidence of vulvar HSIL or vulvar carcinoma, or evidence of HPV-16/18, or subject received non-study related treatment for vulvar HSIL.

Table 4-1: 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 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
Note: The efficacy time frame is defined by samples obtained any time starting from 14 days prior to the protocol-specified target date of Week 48. The first such sample determines the histology endpoint. The most recent HPV clearance result prior to time of the histology sample within the time frame determines the HPV clearance endpoint.	

The number and percentage of subjects with response for the primary endpoint will be presented for each treatment group and compared to historical control separately. A 1-sided p-value and corresponding 2-sided 95% CI using Clopper-Pearson exact binomial methods will be presented for each comparison to prove superiority over historical control. Superiority of VGX-3100 alone or in combination with imiquimod will be declared if 1-sided p-value is <0.025 and the lower end of the CI is greater than 0.02. The primary efficacy will be analyzed separately based on qualifying lesions present at baseline and for all lesions regardless of presence at baseline.

Relevant Output

Table 14.2.1.1A	Primary Efficacy Analysis: Incidence of Histologic Regression and Virologic Clearance at Week 48 (mITT Population)
Table 14.2.1.1B	Primary Efficacy Analysis: Incidence of Histologic Regression and Virologic Clearance at Week 48 (PP Population)
Listing 16.2.6.1	Primary Efficacy Results

4.3.2. Secondary and Exploratory Efficacy Endpoints

Secondary and exploratory efficacy endpoints are supportive to the primary hypothesis.

The following secondary and exploratory efficacy binary endpoints will be presented as percentage point estimates and exact Clopper-Pearson 95% CIs. Each of the following endpoints will be analyzed separately based on qualifying lesions present at baseline and for all lesions regardless of presence at baseline, unless otherwise noted.

- Histologic regression of vulvar HSIL or virologic clearance of HPV-16/18 in vulvar tissue will be assessed at Weeks 74 and 96 by treatment group for all subjects and stratified by subjects who receive 4 or 5 doses (Week 74) and 4, 5, or 6 doses (Week 96).
- Histologic regression of vulvar HSIL will be assessed at Week 48 by treatment group.
- Virologic clearance of HPV-16/18 in vulvar tissue will be assessed at Week 48 by treatment group.
- Histologic regression of vulvar HSIL will be assessed at Weeks 74 and 96 by treatment group for all subjects and stratified by subjects who receive 4 or 5 doses (Week 74) and 4, 5, or 6 doses (Week 96).
- Virologic clearance of HPV-16/18 in vulvar tissue will be assessed at Weeks 74 and 96 by treatment group for all subjects and stratified by subjects who receive 4 or 5 doses (Week 74) and 4, 5, or 6 doses (Week 96).
- Histologic regression of vulvar HSIL to normal tissue will be assessed at Week 48 by treatment group. Normal tissue is defined as having no evidence of vulvar HSIL, no evidence of LSIL (VIN1), and no evidence of condyloma.
- Non-progression of vulvar HSIL to vulvar cancer will be investigated at Week 48 by treatment group. Progression is defined as advancement to carcinoma by histology according to the Pathology Adjudication Committee.
- Virologic clearance of HPV-16/18 outside of the vulva will be assessed at Week 48 by treatment group (for qualifying lesions only) and be presented by anatomic location (cervical, intra anal, oral, and vaginal).
- Histologic regression of vulvar HSIL or virologic clearance of HPV-16/18 in vulvar tissue will be assessed at Weeks 48, 74, and 96 by treatment group.

Reduction in surface area of qualifying vulvar lesion(s) at Weeks 48, 74, and 96 will be assessed by treatment group and determined by quantitative analysis of standardized pre-biopsy photographic imaging. The mean percent change and associated 95% t-distribution based CI will be presented. Also, the percent reduction 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). A lesion will be considered qualifying if it is confirmed to be HPV-16 and/or HPV-18 positive and have histologically confirmed vulvar HSIL by the PAC at screening. The percentage of subjects in each lesion category will be summarized by treatment group with point estimates and associated exact Clopper-Pearson 95% CIs.

Regression/clearance endpoints will be summarized with the number and percentage of subjects meeting the endpoint separately by previous vulvoscopy results and by previous HPV test results. The relationship between the regression/clearance endpoints with miRNA profiles will be summarized with the median change from baseline in miRNA profiles by those who achieved versus not achieved the endpoint.

By-subject listings will be provided for all efficacy-related parameters and results.

Relevant Output

Table 14.2.2.1A	Incidence of Histologic Regression at Week 48 (mITT Population)
Table 14.2.2.1B	Incidence of Histologic Regression at Week 48 (PP Population)
Table 14.2.2.2A	Incidence of Vulvar Virologic Clearance at Week 48 (mITT Population)
Table 14.2.2.2B	Incidence of Vulvar Virologic Clearance at Week 48 (PP Population)
Table 14.2.2.3A	Incidence of Histologic Regression or Virologic Clearance at Week 48 (mITT Population)
Table 14.2.2.3B	Incidence of Histologic Regression or Virologic Clearance at Week 48 (PP Population)
Table 14.2.2.4A	Incidence of Histologic Regression to Normal at Week 48 (mITT Population)
Table 14.2.2.4B	Incidence of Histologic Regression to Normal at Week 48 (PP Population)
Table 14.2.2.5A	Incidence of Non-progression to Vulvar Cancer at Week 48 (mITT Population)
Table 14.2.2.5B	Incidence of Non-progression to Vulvar Cancer at Week 48 (PP Population)
Table 14.2.2.6A	Incidence of Virologic Clearance Outside of the Vulva at Week 48 (mITT Population)
Table 14.2.2.6B	Incidence of Virologic Clearance Outside of the Vulva at Week 48 (PP Population)
Table 14.2.2.7A	Incidence of Histologic Regression and Virologic Clearance at Week 74 and Week 96 (mITT Population)
Table 14.2.2.7B	Incidence of Histologic Regression and Virologic Clearance at Week 74 and Week 96 (PP Population)
Table 14.2.2.8A	Incidence of Histologic Regression at Week 74 and Week 96 (mITT Population)
Table 14.2.2.8B	Incidence of Histologic Regression at Week 74 and Week 96 (PP Population)

Table 14.2.2.19A	Incidence of Virologic Clearance at Week 48 by Previous miRNA Profile (mITT Population)
Table 14.2.2.19B	Incidence of Virologic Clearance at Week 48 by Previous miRNA Profile (PP Population)
Table 14.2.2.20A	Change in Surface Area of Qualifying Vulvar Lesion(s) (mITT Population)
Table 14.2.2.20B	Change in Surface Area of Qualifying Vulvar Lesion(s) (PP Population)
Listing 16.2.6.2A	HPV Testing Results: FFPE Vulvar Tissue Samples
Listing 16.2.6.2B	HPV Testing Results: Cervical ThinPrep and Swab Samples
Listing 16.2.6.3	Cervical Colposcopy and Biopsy Results
Listing 16.2.6.4A	Vulvoscopy and Biopsy Results
Listing 16.2.6.5	Photographic Lesion Results
Listing 16.2.6.6	miRNA Profiles by Visit

4.3.3. Patient-Reported Outcomes

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.

For the SF-36 results, scores and changes from baseline for the 8 subscales (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) as well as the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be summarized using medians and associated exact non-parametric 95% CIs by treatment group.

For the EQ-5D-5L results, the assessment of 5 health categories (1-5 scales) and overall health score, "Your Health Today", (1-100 scale) will be summarized; the scores and changes from baseline will be summarized using medians and associated exact non-parametric 95% CIs, by treatment group.

For the WOMAN-PRO results, 31 self-reported items assessing physical and psychosocial impacts will be summarized. Scores and change from baseline will be summarized for the group of 15 wound-related domain items and the group of 5 difficulties in daily life domain items, the group of 11 psychosocial domain items, and each of the 31 individual items. Medians and associated exact non-parametric 95% CIs will be constructed, by treatment group.

For the 2 additional Global PRO questions assessing quality of life after surgery or biopsy, the time outcome will be summarized with a median and associated exact non-parametric 95% CI, and the binary yes/no outcomes will be summarized with a proportion and associated exact Clopper-Pearson 95% CI, by treatment group.

All PRO data will be presented by study visit in data listings.

Relevant Output

Table 14.2.3.1	Summary of SF-36 Outcomes by Visit (mITT Population)
Table 14.2.3.2	Summary of EQ-5D-5L Outcomes by Visit (mITT Population)
Table 14.2.3.3	Summary of WOMAN-PRO Outcomes by Visit (mITT Population)
Table 14.2.3.4	Summary of Global PRO Outcomes at Week 52 (mITT Population)

Listing 16.2.9.5	Patient Reported Outcomes: SF-36 Results
Listing 16.2.9.6	Patient Reported Outcomes: EQ-5D-5L Results
Listing 16.2.9.7	Patient Reported Outcomes: WOMAN-PRO Results
Listing 16.2.9.8	Global PRO Results

4.3.4. Immunology Endpoints

The following immunology endpoints will be presented in tabulations:

- ELISpot results will be presented by treatment group and scheduled visit, and increase from baseline will be analyzed using an exact non-parametric 95% CI on the median at each time point after baseline (Weeks 15, 27, 48, 74, and 96).
- HPV-16 and HPV-18 E7 specific ELISA results will be presented by treatment group and scheduled visit and analyzed using an exact non-parametric 95% CI on the median at each time point after baseline (Weeks 15, 27, 48, 74, and 96).
- Increase from baseline in frequency of VGX-3100 specific CD8+/CD137+ PBMCs that are Perforin+ will be presented by treatment group and will be analyzed using an exact non-parametric 95% CI on the median.
- Change from baseline in pro-inflammatory and immunosuppressive elements in vulvar tissue, which may include visualization of PD-L1, Granulysin, perforin, CD137, CD103, and possibly other relevant markers, will be presented by treatment group and will be analyzed using a t-distribution based 95% CI on the mean.

All immunology data will be presented by study visit in data listings.

Relevant Output

Table 14.2.4.1A	ELISpot Results by Treatment Group and Scheduled Visit (mITT Population)
Table 14.2.4.1B	ELISpot Results by Treatment Group and Scheduled Visit (PP Population)
Table 14.2.4.2A	HPV-16 and HPV-18 E7 Specific ELISA Results by Treatment Group and Scheduled Visit (mITT Population)
Table 14.2.4.2B	HPV-16 and HPV-18 E7 Specific ELISA Results by Treatment Group and Scheduled Visit (PP Population)
Table 14.2.4.3A	Increase from Baseline in Frequency of VGX-3100 Specific CD8+/CD137+ PBMCs that are Perforin+ by Treatment Group (mITT Population)
Table 14.2.4.3B	Increase from Baseline in Frequency of VGX-3100 Specific CD8+/CD137+ PBMCs that are Perforin+ by Treatment Group (PP Population)
Table 14.2.4.4A	Change from Baseline in Pro-inflammatory and Immunosuppressive Elements in Vulvar Tissue by Treatment Group and Scheduled Visit (mITT Population)

Table 14.2.4.4B	Change from Baseline in Pro-inflammatory and Immunosuppressive Elements in Vulvar Tissue by Treatment Group and Scheduled Visit (PP Population)
Listing 16.2.6.7	Immunologic Assay Collection
Listing 16.2.6.8A	Immunologic Results: ELISA and ELISpot
Listing 16.2.6.8B	Immunologic Results: Flow Cytometry
Listing 16.2.6.8C	Immunologic Results: Pro-inflammatory and Immunosuppressive Elements in Vulvar Tissue

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population and will be presented based on actual treatment received.

4.4.1. Study Drug Exposure

Study drug exposure will be tabulated by the number of doses received. The number and percentage of subjects will be reported by treatment group and overall.

Compliance will be measured by the following parameters: incorrect treatment received, unsuccessful EP, the location of the EP treatment, the size of EP array, and whether or not a guide was used.

Dosing information for each subject will be presented in a data listing.

Relevant Output

Table 14.3.5.1	Study Drug Exposure (Safety Population)
Listing 16.2.5.1	Study Drug Administration
Listing 16.2.5.2	Electroporation Administration
Listing 16.2.5.3	Electroporation Issue Reports
Listing 16.2.5.4	Electroporation Guide Use

4.4.2. Adverse Events

All AEs will be coded using the most current version of the MedDRA coding system and displayed in tables and data listings using system organ class (SOC) and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset after the administration of study medication through the end of the study (i.e., study discharge).

An AESI is defined as an AE deemed related to VGX-3100 delivered with CELLECTRA™ 2000 that requires expedited communication from the site to the Sponsor and meets any of the following criteria per the Toxicity Grade for Healthy Adults:

- 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.

Separate summaries of AEs will be presented by treatment group and overall for events with an onset within the first 28, 14, and 7 days after injection and overall. The summary will include the number and percentage of subjects with any treatment-emergent AE (TEAE), with any TEAE assessed by the Investigator as related to treatment, with any AESI, with any TEAE by Common Terminology Criteria for Adverse Events (CTCAE v4.03) grade, with any SAE, with any pre-treatment AE, with any AE leading to discontinuation of treatment, and with any AE leading to death.

In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidences in the analysis, regardless of the number of episodes. In addition to the number of subjects that experienced at least 1 of the events, the total number of events observed across subjects will also be reported.

Summary tables by SOC and preferred term will be produced for the following, presented by treatment group:

- All TEAEs
- All TEAEs by most recent injection
- All TEAEs by severity grade
- All TEAE assessed as at least possibly related to treatment by the Investigator (i.e., treatment-related)
- All TEAEs with onset within 7 days of an injection
- All TEAEs with onset within 7 days by severity grade
- All treatment-related TEAEs with onset within 7 days of an injection
- All TEAEs with onset within 14 days of an injection
- All TEAEs with onset within 14 days of an injection by severity grade
- All treatment-related TEAEs with onset within 14 days of an injection
- All TEAEs with onset within 28 days of an injection
- All TEAEs with onset within 28 days of an injection by severity grade
- All treatment-related TEAEs with onset within 28 days of an injection

For each tabulation, TEAEs are summarized by proportions of subjects; therefore, in any tabulation, a subject contributes only once to the count for a given TEAE (SOC or preferred term), irrespective of the number of episodes of a particular AE term reported. Injection site reactions are included in the TEAE summaries.

The frequency of subjects with preferred term events with onset within 7, 14, or 28 days separately will be summarized with percentages and exact Clopper-Pearson 95% CIs. All AEs occurring on-study will be listed in subject data listings. By-subject listings also will be

provided for the following: AEs leading to death, SAEs, AEs with severity ≥ Grade 3, AEs leading to discontinuation of treatment, and AESIs.

Relevant Output

Table 14.3.1.1A	Overall Summary of Adverse Events (Safety Population)
Table 14.3.1.1B	Overall Summary of Treatment-Emergent Adverse Events with Onset within 7 Days of an Injection (Safety Population)
Table 14.3.1.1C	Overall Summary of Treatment-Emergent Adverse Events with Onset within 14 Days of an Injection (Safety Population)
Table 14.3.1.1D	Overall Summary of Treatment-Emergent Adverse Events with Onset within 28 Days of an Injection (Safety Population)
Table 14.3.1.2A	Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2B	Treatment-Emergent Adverse Events with Onset within 7 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2C	Treatment-Emergent Adverse Events with Onset within 14 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2D	Treatment-Emergent Adverse Events with Onset within 28 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3A	Treatment-Emergent Adverse Events by Most Recent Injection, MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3B	Treatment-Emergent Adverse Events with Onset within 7 Days of Each Injection by Most Recent Injection, MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3C	Treatment-Emergent Adverse Events with Onset within 14 Days of Each Injection by Most Recent Injection, MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3D	Treatment-Emergent Adverse Events with Onset within 28 Days of Each Injection by Most Recent Injection, MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.4A	Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Severity Grade (Safety Population)
Table 14.3.1.4B	Treatment-Emergent Adverse Events with Onset within 7 Days of an Injection by MedDRA System Organ Class, Preferred Term, and Severity Grade (Safety Population)
Table 14.3.1.4C	Treatment-Emergent Adverse Events with Onset within 14 Days of an Injection by MedDRA System Organ Class, Preferred Term, and Severity Grade (Safety Population)

Table 14.3.1.4D	Treatment-Emergent Adverse Events with Onset within 28 Days of an Injection by MedDRA System Organ Class, Preferred Term, and Severity Grade (Safety Population)
Table 14.3.1.5A	Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.5B	Treatment-Related Adverse Events with Onset within 7 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.5C	Treatment-Related Treatment-Emergent Adverse Events with Onset within 14 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.5D	Treatment-Related Treatment-Emergent Adverse Events with Onset within 28 Days of an Injection by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.1	Listing of Adverse Events Leading to Death (Safety Population)
Table 14.3.2.2	Listing of Serious Adverse Events (Safety Population)
Table 14.3.2.3	Listing of Adverse Events with CTCAE Toxicity ≥ Grade 3 (Safety Population)
Table 14.3.2.4	Listing of Adverse Events Leading to Discontinuation of Treatment (Safety Population)
Table 14.3.2.5	Listing of Adverse Events of Special Interest (Safety Population)
Listing 16.2.7.1	Adverse Events by Subject, MedDRA Preferred Term, and Verbatim Term
Listing 16.2.7.2	Adverse Events by MedDRA System Organ Class/Preferred Term and Subject
Listing 16.2.7.3	Glossary of Adverse Events

4.4.3. Laboratory Data

Clinical laboratory values will be expressed in International System (SI) units.

Clinical laboratory data will be collected at screening. All laboratory data will be provided in by-subject data listings, including hematology, clinical chemistry, creatinine phosphokinase, urinalysis, and pregnancy testing assessments.

Relevant Output

Listing 16.2.8.1	Laboratory Results: Hematology
Listing 16.2.8.2	Laboratory Results: Serum Chemistry
Listing 16.2.8.3	Laboratory Results: Urinalysis
Listing 16.2.8.4	Laboratory Results: Creatine Phosphokinase
Listing 16.2.8.6	Laboratory Results: Pregnancy

4.4.4. Vital Signs and Physical Examination

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs.

Physical examination results at each on-study evaluation will be summarized.

All physical examination findings and vital sign measurement will be presented in by-subject data listings.

Relevant Output

Table 14.3.5.2	Summary of Actual Value and Change from Baseline for Vital Signs by Scheduled Visit (Safety Population)
Table 14.3.5.3	Physical Examination Results by Scheduled Visit (Safety Population)
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	Physical Examination Findings

4.4.5. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening for all subjects and results will be provided in a by-subject data listing. The ECG results include ventricular rate and PR, QRS, QT, QTcB (calculated by the Bazett correction formula), ST Segment, and T-wave. QTcB will be calculated using the formula $QT/\sqrt{RR}$. The RR interval will be derived as 60 divided by the ventricular rate. All abnormal results and clinical significance will be flagged within listing.

Relevant Output

Listing 16.2.9.3	12-Lead Electrocardiogram Results

4.4.6. Prior and Concomitant Medications

Concomitant medications include all medications taken or medical procedures performed with a stop date that is on or after the date of first dose of study drug. The number and percentage of subjects with medications at anatomic therapeutic class (ATC) Class Level 3 and Preferred Term levels will be reported by treatment group and overall. Prior and concomitant medications will be presented separately.

The use of concomitant medications, including medications used for management of anxiety or pain due to the EP procedure, will be included in a by-subject data listings.

Relevant Output

Table 14.3.5.4	Prior Medications (Safety Population)
Table 14.3.5.5	Concomitant Medications (Safety Population)
Listing 16.2.9.4A	Prior Medications
Listing 16.2.9.4B	Concomitant Medications

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this SAP.

6. REFERENCES

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7. STATISTICAL OUTPUT

7.1. List of Statistical Output to be Generated

The lists of statistical output are provided in separate documents for statistical tables and data listings.

7.2. Statistical Table Shells

Statistical table shells are provided in a separate document.

7.3. Data Listing Shells

Data listing shells are provided in a separate document.