Official Title:	**A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 Related Anal or Anal/Peri-Anal, High Grade Squamous Intraepithelial Lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in Individuals That Are Seronegative for Human Immunodeficiency Virus (HIV)-1/2**
NCT Number:	NCT03499795
Document Dates:	Statistical Analysis Plan Version 1.0: 09 November 2021

STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462, USA Tel: (267) 440-4200 Fax: (267) 440-4242
SPONSOR REPRESENTATIVE:	[redacted], PhD [redacted]
PROTOCOL TITLE:	A Phase 2, Open Label, Study of VGX-3100 Delivered Intramuscularly (IM) Followed by Electroporation (EP) for the Treatment of HPV-16 and/or HPV-18 related Anal or Anal/Peri-anal, High grade squamous intraepithelial lesion (HSIL), (AIN2, AIN3, PAIN2, PAIN3) in individuals that are seronegative for Human Immunodeficiency Virus (HIV)-1/2
PROTOCOL NUMBER:	HPV-203
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NAME OF TEST DRUG:	VGX-3100
PHASE:	Phase 2a
METHODOLOGY:	Multi-center, Single-Arm, Open-Label
ANALYSIS PLAN DATE:	27 Oct 2021
ANALYSIS PLAN VERSION:	Final Version 1.0
AUTHOR:	[redacted]

APPROVAL SIGNATURE PAGE

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

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Protocol Number: HPV-203

Document Date / Version: 27 Oct 2021 / Final Version 1.0

Veristat, Inc. Author: [redacted], MS

[redacted]

Approval Signature	Job Title

Sponsor Signatory: [redacted], PhD
[redacted]

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.

Approval Signature	Job Title

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CL	Clearance
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
QTc interval	QT interval corrected for heart rate
Rel Day	Relative study day
SAP	Statistical analysis plan
SD	Standard deviation
SI	International System of Units
VC	Vital capacity
WHO	World Health Organization

1.1. Introduction and Objectives

1.1.1. Introduction

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the ano-genital area and aero-digestive tract, in both men and women. Human papillomavirus types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). In the United States (US), approximately 14 million new genital HPV infections occur annually, and approximately half of these infections are with a high-risk HPV type (HR-HPV) and thus can cause cancer [1]. In U.S. adults through age 59 years, about 25% of men and 20% of women have genital HR-HPV infection [2]. Human papillomavirus causes more cancers than any other virus. In US archival tissues of cancers diagnosed from 1993 to 2005, HPV deoxyribonucleic acid (DNA) was detected in 68.8% of vulvar, 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (OP), 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS) [3]. An average of over 30,000 cases per year of HPV-attributable cancer were diagnosed during the period from 2008 through 2012 in the US [4]. Human papillomavirus-16 and HPV-18 are the most significant among HR types since they are responsible for most HPV-caused cancers [3].

With regard to anal cancer, about 95% of cases are caused by HPV, and most of those cases are caused by HPV-16 [5,6]; with some caused by HPV-18 and perhaps other HPV genotypes [1]. An estimated 8,300 new cases of anal cancer in the US are diagnosed each year (for 2017), with an estimated 1,280 deaths annually due to this cancer [7]. In Canada, the latest available data is for 2013, during which 580 new cases of anal cancer were diagnosed and 144 persons died due to anal cancer [8].

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

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

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 to answer the study objectives. 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

1.1.5.1. Primary Objectives

The primary objective is to determine the efficacy of 3 doses of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18.

1.1.5.2. Secondary Objectives

The secondary objectives include the following:

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

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

1.1.5.3. Exploratory Objectives

The exploratory objectives include the following:

- To describe the long-term efficacy of VGX-3100 with respect to combined histopathologic regression of anal or anal/peri-anal HSIL and virologic clearance of HPV-16 and/or HPV-18
- To describe the long-term efficacy of VGX-3100, as measured by histologic regression of anal or anal/peri-anal HSIL
- To describe the long-term efficacy of VGX-3100, as measured by virologic clearance of HPV-16 and/or HPV-18 by testing from lesion tissue
- To describe the long-term efficacy of VGX-3100, as measured by virologic clearance of HPV-16 and/or HPV-18 by intra-anal swab testing
- To evaluate tissue immune responses to VGX-3100 in intra-anal and/or peri-anal samples
- To describe the clearance of HPV-16 and/or HPV-18 infection from non-anal anatomic locations
- To describe the association of microRNA (miRNA) profile, previous anoscopy, cytology, and HPV testing results with Week 36 histologic regression
- To describe the patient reported outcomes (PRO) for subjects treated with VGX-3100
- To determine the humoral and cellular immune response following administration of VGX-3100 at post dose 3, and after additional dosing compared to baseline
- To determine the long-term efficacy of VGX-3100 with respect to histopathologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16 and/or HPV-18

1.2. Study Design

1.2.1. Synopsis of Study Design

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

HSIL associated with HPV-16 and/or HPV-18. Approximately 24 subjects will receive at least 3 doses of VGX-3100. Each dose of VGX-3100 will be administered IM in a 1-mL volume followed immediately by EP.

To be eligible for the study, subjects must consent to participate and agree to the collection of anal lesion tissue samples for anal cytology and genotyping, a Digital Anal Rectal Examination (DARE), blood samples for immunologic assessments, high-resolution anoscopy (HRA) and HRA-guided biopsies. All intra-anal and/or peri-anal lesion(s) of adequate size (≥ 4mm) will be biopsied at Screening. Biopsy slides will be sent to a Pathology Adjudication Committee (PAC) for evaluation before enrollment. To be eligible for enrollment, the PAC must assign the diagnosis of anal or anal/peri-anal HSIL (AIN2, AIN3, PAIN2, PAIN3) based on the biopsy sample(s). Subjects must also have intra-anal and/or peri-anal lesion tissue test positive for HPV genotype 16 and/or 18 to be eligible for participation in the study.

Depending upon their disposition with regard to histologic and lesion area changes during the trial, all eligible subjects who consent to participate in the HPV-203 study will receive at least three doses of VGX-3100 (6 mg in 1 mL) administered IM (deltoid, preferred site, or anterolateral quadriceps, alternate site), each followed immediately by EP with the CELLECTRA™ 5PSP device. The first study treatment will be administered on Day 0, the second at Week 4, and the third at Week 12. Partial response to VGX-3100 may still be of medical importance by being able to limit the extent of surgery necessary. For partial responders at Week 36, a fourth dose may be administered at Week 40.

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, 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 to 88 weeks for the treatment and follow-up periods.

1.2.2. Randomization Methodology

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

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, 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):

- If at any time during a study one-third (1/3) or more of the subjects experience an adverse event of special interest (AESI), verified per protocol definition

- If any serious adverse event (SAE; or potentially life-threatening adverse event [AE]) or death verified as related to study treatment occurs
- If 3 or more subjects in this study 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

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

.

Table 1: Schedule of Assessments

Study Action	Screening (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Informed consent	X												
Medical History/Demographics	X												
Medications (prior/concomitant)	X	X		X		X	X	X	X	X		X	X
Socio-behavioral assessment	X								X			X[15]	X
Inclusion/Exclusion criteria[1]	X	X											
Physical exam (PE)/assessment [2]	X	X		X		X	X	X	X	X		X	X
Vital signs	X[3]	X		X		X	X	X	X	X		X	X
Screening safety (12 lead ECG, laboratories) [4]	X												
Pregnancy Testing [5]	X	X		X		X	X	X	X	X		X	X
HIV Ab by ELISA	X								X				
Blood immunologic samples	X[6]	X[6]					X[7]		X[6]				X[6]
Oropharyngeal (OP) rinse		X		X			X	X	X			X	X
Vaginal, cervical, and penile swab		X		X			X	X	X			X	X
Intra-anal and/or peri-anal swab	X	X		X			X	X	X			X	X
Digital Anal Rectal Examination DARE [8]	X	X		X			X	X	X			X	X
High Resolution Anoscopy (HRA) [9]	X	X		X			X	X	X			X	X
Lesion photography [10]	X	X		X			X	X	X			X	X
Biopsy [11]	X								X			X[18]	

Study Action	Screening (-10 wk. to -1d)	Day 0	8-14 days post dose 1 Phone Call	Week 4 (± 4 days)	8-14 days post dose 2 Phone Call	Week 12 (± 4 days)	Week 15 (± 1 Week)	Week 28 (± 1 Week)	Week 36 (± 1 Week)	Week 40 (± 1 Week)	8-14 days post dose 4 Phone Call	Week 64 (± 2 Weeks)	Week 88 (± 2 Weeks)
Inject VGX-3100 +EP [12]		X		X		X				X[12]			
Post treatment reaction assessment		X		X		X				X			
Distribute Participant Diary Card (PDC)		X		X		X				X			
Review PDC [13]			X		X		X				X	X	
Patient Reported Outcomes (PROs) (SF-36v2™) (EQ-5D-5L)[14]		X[16]	X	X	X	X	X		X	X	X[17]	X	X

1. Subject eligibility will be reconfirmed at every visit.
2. Full physical exam (PE) mandatory at Screening and study discharge (Week 88), otherwise targeted PE as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE.
3. Screening vital signs must include a measured height and weight and calculated body mass index (BMI) (Bodyweight in kilograms divided by height in meters squared). Weight will be collected at all dosing visits.
4. Screening 12-lead electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, alanine aminotransferase (ALT), and creatine phosphokinase (CPK) performed within 45 days before first dose administration.
5. Negative spot urine pregnancy test is required for female subjects at Screening, before each study treatment, high-resolution anoscopy (HRA), and biopsy/surgical excision; the pregnancy test at Week 40 would only be needed for subjects who receive an additional dose.
6. 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 before first dose.
7. At least 51 mL (6 x 8.5-mL yellow [ACD] tubes) whole blood and 4 mL serum should be collected at Week 15.
8. Digital Anal Rectal Examinations (DARE) are to be performed once cytology has been collected and before HRA.
9. An additional visit may be scheduled to perform HRA if worsening of disease is suspected. Biopsies should not be performed at any visit other than at entry (Screening) and Weeks 36 and 64 for Subgroup C unless the Investigator suspects invasive cancer. All biopsy samples and/or excision samples must be sent to the Pathology Adjudication Committee (PAC) for review.
10. Photography of qualifying lesion(s) must be performed before and after biopsy, and at all HRA examinations. If a pre-biopsy digital photograph is not available for a historical biopsy sample at Screening, a post-biopsy photo will be sufficient. Photographs of intra-anal lesion(s) will be for documentation purposes only. All qualifying peri-anal lesion(s) will be assessed using the ruler provided. The ruler should be placed in the field of vision and should be documented with photography at Screening, Day 0, and Weeks 4, 15, 28, 36, 64, and 88.
11. Tissue specimens (paraffin blocks) from all excised tissue lesion(s) that led to eligibility at study entry must be reviewed by the PAC, and residual tissue from entry and Weeks 36 and 64 specimen(s) (paraffin blocks) must be sent to the central laboratory for immune analysis and Human Papillomavirus (HPV) testing.
12. Potential dosing at Week 40 is applicable for partial responders only.
13. A phone call will be used to review the Participant Diary Card (PDC) with subjects within 8-14 days after doses 1 and 2. The subject will be expected to bring the PDC to the next visits for review. Subjects who receive an additional fourth dose will also have a phone call 8-14 days post dose 4 where the PDC will be reviewed. The subject should bring the PDC to the next visit.
14. Patient-reported outcome (PRO) measures (SF-36v2™ and EQ-5D-5L), plus 2 additional "global" questions will be assessed as described in Section 6.13 of the protocol.
15. This socio-behavioral assessment will only apply to those subjects in Subgroup C who receive a fourth dose of investigational product.
16. PROs at this time point must be administered before first dose of study drug.
17. PROs at this time point will only be for subjects who received a fourth dose of study drug.
18. Under Protocol Amendment 3.0, in additional to HSIL lesion(s) found at Screening, all visible lesions should have biopsy obtained at Week 64 and sent to the central pathology lab for review by PAC.

1.2.5. Efficacy, Pharmacokinetic, and Safety Parameters

1.2.5.1. Efficacy Parameters

The primary efficacy endpoint is the proportion of subjects with combined response outcome of histologic regression of anal or anal/perianal HSIL and virologic clearance of HPV-16/18 in intra-anal and/or peri-anal lesion tissue at Week 36. Histologic regression is defined as no evidence of anal or anal/peri-anal HSIL on histology. Virologic clearance is defined as no evidence of HPV-16 and/or HPV-18 by specific HPV testing.

Secondary efficacy endpoints are:

- Proportion of subjects with histologic regression at Week 36.
- Proportion of subjects with virologic clearance from intra-anal and/or peri-anal lesion tissue by type-specific HPV testing at Week 36.
- Proportion of subjects with virologic clearance from intra-anal swab by specific HPV testing at Week 36.
- Proportion of subjects with no evidence of anal or anal/peri-anal low-grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of AIN2, AIN3, PAIN2, PAIN3) on histology (i.e., biopsies or excisional treatment) at Week 36.
- Proportion of subjects with no progression of anal or anal/perianal HSIL to carcinoma from baseline on histology (i.e., biopsies or excisional treatment) at Week 36.
- Proportion of subjects with histologic regression or virologic clearance at Week 36 from intra-anal and/or peri-anal lesion tissue.
- Percent reduction in the number of qualifying intra-anal and/or perianal lesion(s) and the size of peri-anal lesion(s) as determined by the Investigator at Weeks 36, 64, and 88 compared with baseline. Results will also be classified as follows: 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).

Exploratory efficacy endpoints are:

- Proportion of subjects with histologic regression and virologic clearance at Week 64 by testing from intra-anal and/or peri-anal lesion tissue.
- Proportion of subjects with histologic regression at Week 64.
- Proportion of subjects with virologic clearance by testing from intra-anal and/or peri-anal lesion tissue at Week 64.
- Proportion of subjects with virologic clearance from intra-anal swab by specific HPV testing at Week 64 and Week 88.

- Proportion of subjects with virologic clearance from non-anal anatomic locations at Week 36.

- The relationship of miRNA profile (baseline and at Weeks 15 and 36), previous anoscopy, cytology and HPV testing results with histologic regression of anal or anal/peri-anal HSIL at Week 36.

- Proportion of subjects with histologic regression or virologic clearance from intra-anal and/or peri-anal tissue at Week 64.

To assess quality of life and related impacts on subjects, PRO instruments will be administered and will include the SF-36v2™, the EQ-5D-5L, and additional PRO questions assessing quality of life after surgery or biopsy.

- SF-36v2™ - generically measures functional health and well-being, for physical and mental health; 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 & general health status; consists of 6 items covering 6 domains (Mobility, Selfcare, Usual activity, Pain/discomfort, Anxiety/depression, and Global health status)

1.2.5.2. Immunology Parameters

A secondary immunology endpoint is the flow cytometry response magnitude from the Lytic Granule Loading assay at baseline and Week 15 visits. 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).

Exploratory immunology endpoints include the following:

- Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at baseline and Weeks 15, 36, and 88 visits

- Interferon-γ ELISpot response (spot forming units [SFU]) at baseline and Weeks 15, 36, and 88 visits.

- Proinflammatory and immunosuppressive elements results including, but not limited to, CD8+ and FoxP3+ infiltrating cells as well as Granulysin, Perforin, CD137, CD103 and PD-L1 in intra-anal and/or peri-anal tissue as sample allows.

1.2.5.3. Safety Parameters

Safety evaluations performed during the study included physical examinations, measurement of vital signs, 12-lead ECGs, clinical laboratory evaluations including hematology, serum chemistry, and CPK, and monitoring of AEs, including injection site reactions.

The secondary safety endpoints are:

- Local and systemic events for 7 days after each dose as noted in the Participant Diary Card
- All AEs including SAEs, unanticipated (serious) adverse device effect, and other unexpected AEs for the duration of the study (through the Week 88 visit)

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.
- Per-protocol (PP) Population: All subjects who receive all doses of VGX-3100 + EP and have no protocol violations. Subjects excluded from the PP population will be identified and documented before locking of the study database.
- Safety Population: All subjects who receive at least 1 dose of VGX-3100 + EP.

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, major protocol violations, as determined by a review of the data before locking of the study database and the conduct of statistical analyses, may 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 that warrants exclusion from the PP population. This file will be finalized before hard database lock.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

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

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 which is designated as Day 1. The preceding day is Day -1, the day before that is 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 Council for 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 (with a category for missing data) 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 overall as applicable.

Formal statistical hypothesis testing will be performed on the primary endpoint compared with historical control at the 1-sided, 0.05 level of significance. Summary statistics will be presented, as well as 2-sided confidence intervals (CIs) on selected parameters, as described in the sections below.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or higher, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Mar 2016 LT.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement before 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

Multiplicity is not of concern for this study with a single primary efficacy endpoint.

3.8. Subpopulations

Week 64 and Week 88 exploratory efficacy endpoints will be additionally analyzed according to number of doses received (3 vs 4).

3.9. Withdrawals, Dropouts, Loss to Follow-up

If more than 10% of subjects who receive study treatment discontinue before the Week 36 primary endpoint procedures, then supplementation of study subjects will be considered.

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 was used and has a stop date before the start of the trial (before 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. In data listings, the relative day of all dates will be presented.

The efficacy time frame for histopathologic regression and virologic clearance is defined as any time starting from 14 days before the protocol-specified visit week.

3.12. Interim Analyses

For reasons of futility (early evidence of poor efficacy of VGX-3100) or safety issues, the DSMB could recommend stopping enrollment at any time. However, no formal interim analyses will be performed for this study, 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 and include the number screened, the number treated in total, 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, and the number who withdrew before completing the study 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. Eligibility based on the inclusion /exclusion criteria and inclusion in the study populations will also be provided in listings.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history will be summarized and presented. 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 ethnicity and race category also will be presented. Results at Screening for anal or anal/peri-anal HSIL 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 electronic case report form. Prior anal disease, HPV diagnoses, and reproductive history will be presented in data listings as well as tobacco history and alcohol use.

Data for each subject will also be provided in data listings.

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 endpoint is the combined response outcome of histologic regression of anal or anal/perianal HSIL and virologic clearance of HPV-16/18 in intra-anal and/or peri-anal lesion tissue at Week 36. Histologic regression is defined as no evidence of anal or anal/peri-anal HSIL on histology. Virologic clearance is defined as no evidence of HPV-16 and/or HPV-18 from intra-anal and/or peri-anal tissue by type-specific HPV testing. A treatment responder is defined as a subject with no histologic evidence of anal or anal/peri-anal HSIL and no evidence of HPV-16 or HPV-18 in anal lesion tissue and who did not receive any non-study treatment of curative intent of intra-anal and/or peri-anal lesions. A treatment non-responder is defined as a subject with histologic evidence of anal or anal/peri-anal HSIL, adenocarcinoma-in-situ, or anal or anal/peri-anal carcinoma, a subject with evidence of HPV-16/18 in anal lesion tissue, or a subject who received non-study treatment of curative intent of intra-anal and/or peri-anal lesions.

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

Responder	**Non-Responder**
• No histologic evidence of anal or anal/peri-anal HSIL in qualifying or new lesions AND • Negative PCR for HPV-16 or HPV-18 in anal lesion tissue in qualifying or new lesions AND • No non-study treatment of curative intent of intra-anal and/or peri-anal lesions	• Histologic evidence of anal or anal/peri-anal HSIL, anal adenocarcinoma-in-situ, anal or anal/peri-anal carcinoma in qualifying or new lesions OR • PCR positive for HPV-16 or HPV-18 in anal lesion tissue in qualifying or new lesions OR • Any non-study treatment of curative intent of intra-anal and/or peri-anal lesions
Note: The efficacy time frame is defined by samples obtained any time starting from 14 days before the protocol-specified target date of Week 36. The first such sample determines the histology endpoint. The most recent HPV clearance result before time of the histologic and lesion 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 and compared to historical control. A 1-sided p-value and corresponding 1-sided 95% CI using Clopper-Pearson exact binomial methods will be presented to prove superiority over historical control. Superiority of VGX-3100 will be declared if the 1-sided p-value is <0.05 and the lower end of the CI is greater than 0.15. Primary efficacy will be analyzed separately based on qualifying lesions present at baseline and for all lesions regardless of presence at baseline.

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 2-sided 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 anal or anal/peri-anal HSIL and virologic clearance of HPV-16/18 in intra-anal and/or peri-anal lesion tissue will be assessed at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses.

- Histologic regression of anal or anal/peri-anal HSIL or virologic clearance of HPV-16/18 in intra-anal and/or peri-anal lesion tissue will be assessed at Week 36 for all subjects and separately at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses.

- Histologic regression of anal or anal/peri-anal HSIL will be assessed at Week 36 for all subjects and separately at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses.

- Virologic clearance of HPV-16/18 will be assessed by testing from intra-anal and/or peri-anal lesion tissue at Week 36 for all subjects and separately at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses.

- Virologic clearance of HPV-16/18 will be assessed by intra-anal swab testing at Week 36 for all subjects and separately at Weeks 64 and 88 for all subjects and also stratified by subjects who receive 3 or 4 doses.

- Virologic clearance of HPV-16/18 will be assessed on specimens from non-anal anatomic locations as applicable based upon gender (i.e., oropharynx, cervical, vaginal, and penile) at Week 36 for all subjects.

- Complete histopathologic regression of anal or anal/peri-anal HSIL to normal tissue will be assessed at Week 36 for all subjects and separately at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses. Normal tissue is defined as having no evidence of anal or anal/peri-anal LSIL or HSIL (AIN2, AIN3, PAIN2, PAIN3).

- Non-progression of anal or anal/peri-anal HSIL will be investigated at Week 36 for all subjects and separately at Week 64 for all subjects and also stratified by subjects who receive 3 or 4 doses. Progression is defined as advancement to carcinoma by histology according to the PAC.

Reduction in surface area of qualifying intra-anal and/or peri-anal lesion(s) at Weeks 36, 64, and 88 will be assessed and determined by quantitative analysis of standardized pre-biopsy digital photographic imaging. The mean percent change and associated 95% t-distribution based CI will be presented. A lesion will be considered qualifying if it is confirmed to be HPV-16 and/or HPV-18 positive and is histologically confirmed as intra-anal and/or peri-anal HSIL by the PAC at Screening.

The relationship between regression/clearance endpoints at Week 36 will be summarized with the number and percentage of subjects meeting the endpoint separately by previous HRA results, previous cytology results, and previous HPV test results. The relationship between the

regression/clearance endpoints at Week 36 with miRNA profiles will be summarized with the median change from baseline in miRNA profiles by those who achieved versus those who did not achieve the endpoint. A subject's miRNA profile is based on change from baseline normalized result to the latest normalized result obtained before the time of the Week 36 endpoint.

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

4.3.3. Patient-Reported Outcomes

PRO assessments will be performed at Day 0 before first dose, on the day of and after each dose, and at Weeks 36, 64, and 88. There will be an additional PRO assessment at Week 40 if a subject receives a fourth dose.

For the SF-36v2 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.

For the EQ-5D-5L results, the scores for 5 health categories (1-5 scales) and overall health score (1-100 scale) will be summarized; the scores and changes from baseline will be summarized using medians and associated exact non-parametric 95% CIs.

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.

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

4.3.4. Immunogenicity Endpoints

The following immunology endpoints will be analyzed:

- ELISpot results will be presented by 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, 36, and 88).
- HPV-16 and HPV-18 E7-specific ELISA results will be presented by scheduled visit and analyzed using geometric mean titers and t-distribution 95% CI on the geometric mean titer at each time point after baseline (Weeks 15, 36, and 88).
- Increase from baseline in frequency of VGX-3100-specific CD8+/CD137+ peripheral blood mononuclear cells that are Perforin+ will be analyzed using an exact non-parametric 95% CI on the median.

- Change from baseline in proinflammatory and immunosuppressive elements in tissue based on nanostring assays will be analyzed using a t-distribution based 95% CI on the mean.

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

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population.

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.

Compliance will be measured by the following parameters: success of 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.

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™ 5PSP 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 fewer
- Grade 3 or greater systemic symptoms, including generalized pruritus

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

- 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 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 days and, separately, within 28 days after dosing 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.

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, CPK, and urine pregnancy testing assessments.

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 measurements will be presented in by-subject data listings.

4.4.5. Electrocardiogram

A 12-lead 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, QRS axis, QT, QT corrected for heart rate (QTc) (calculated by the Bazett's formula [QTcB] or Fridericia's formula [QTcF]), ST Segment, and T-wave. The RR interval will be derived as 60 divided by the ventricular rate. Investigator assessment of whether the ECG is normal or abnormal will also be included. All abnormal results and clinical significance will be flagged within the listing.

4.4.6. Prior and Concomitant Medications

Prior medications are those that were used and stopped before the start of the trial (before Day 0). Concomitant medications include all medications taken 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. 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 listing.

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 statistical analysis plan.

6. REFERENCES

1. Humans IWGotEoCRt. Biological agents. Volume 100 B. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012,**100**:1-441.

2. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in Adults Aged 18-69: United States, 2011-2014. *NCHS Data Brief* 2017:1-8.

3. Centers for Disease C, Prevention. Human papillomavirus-associated cancers - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep* 2012,**61**:258-261.

4. Viens LJ, Henley SJ, Watson M, Markowitz LE, Thomas CC, Thompson TD*, et al.* Human Papillomavirus-Associated Cancers - United States, 2008-2012. *MMWR Morb Mortal Wkly Rep* 2016,**65**:661-666.

5. National Cancer Institute. Fact Sheet: HPV and Cancer. In; 2015.

6. Bruni L, Barrionuevo-Rosas L, Alberto G, Serrano B, Mena M, Gomez D*, et al.* Human Papillomavirus and Related Diseases Report in USA. In: ICO Information Centre on HPV and Cancer (HPV Information Centre); 2017.

7. National Cancer Institute SEER Program. Cancer Stat Facts: Anal Cancer. In; 2017.

8. Canadian Cancer Society. Anal Cancer Statistics. In; 2017.

7. CLINICAL STUDY REPORT APPENDICES

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.

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Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 08-Nov-2021 17:58:56 GMT+0000

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