Official Title: **PROSPECTIVE STUDY OF HPV SPECIFIC IMMUNOTHERAPY IN SUBJECTS WITH HPV ASSOCIATED HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCCa)**

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Prospective Study of HPV Specific Immunotherapy in Subjects with HPV Associated Head and Neck Squamous Cell Carcinoma (HNSCCa)

Principal Investigator:
[redacted], MD, MPH

Protocol Version 2.1

Medical Oncology
[redacted], MD
[redacted], MD
[redacted], MD

Head and Neck Surgery
[redacted] Jr, MD
[redacted], MD
[redacted], MD
[redacted], MD
[redacted], MD

Radiation Oncology
[redacted], MD
[redacted], MD
[redacted], MD

Basic Science Expert
[redacted], PhD

Research Correlative Studies
[redacted], MD, PhD

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

Research Correlative Studies
[redacted], PhD

Biostatistics
[redacted], PhD

Medical Monitor
[redacted], MD

IND # 15946, under Inovio, Inc.

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SUMMARY OF CHANGES

The following is a list of significant protocol changes from v2.0 dated June 25, 2015 to v2.1 dated April 8, 2016. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol.

1. The long term follow up period post last dose is changed from "2 years from screening" to "6 months post the last dose of immunotherapy". It is mainly because to date, safety profile from 19 subjects who have been followed for more than 6 months does not show any study treatment related adverse safety events, therefore it is considered an undue burden on subjects to continue the follow up for an extended time period.
   Following sections of the protocol are affected:

   - Protocol Synopsis
   - Tables S1 and S2 Schedule of Events
   - Section 3, Study Design
   - Section 6.1.7 Cohort I Long Term Follow Up
   - Section 6.2.4 Cohort II, Long Term Follow Up

PROTOCOL ACKNOWLEDGEMENT

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

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and proved the necessary assurances that this study will be conducted according to The Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____	_____	_____
Investigator's printed name	Signature	Date

_____	_____
Medical Monitor	Date

Protocol Number: HPV-005
Site Number:
Version Number/Version Date: v2.1 /8-April-2016

Table of Contents

CLINICAL PROTOCOL SYNOPSIS

Title of Study: Prospective Study of HPV Specific Immunotherapy in Subjects with HPV Associated Head and Neck Squamous Cell Carcinoma (HNSCCa)

Number of Study Centers and Countries/Regions: 1 Site (United States)

Research Hypothesis: This protocol proposes to study the safety and the immune effects of immunotherapy with INO-3112 that contains VGX-3100, synthetic plasmid DNA encoding human papillomavirus (HPV)-16 and HPV-18 E6/E7 antigens and INO-9012, a recombinant IL-12 molecular adjuvant administered.

The safety and effects of immunotherapy will be studied in following two populations:

1. In chemo- and radiation-naïve subjects who undergo definitive surgery and
2. In subjects after chemoradiation therapy

Study Objectives:

Primary: Evaluate safety of treatment with INO-3112.

Secondary:

1. Evaluate humoral and cellular immune response post to administration of INO-3112 in chemo- and radiation-naïve subjects who undergo definitive surgery:
    a. Pre- and Post-immunotherapy tissue analysis to evaluate infiltration of T cells in the tumor
    b. Evaluate effect of number of doses on immune responses
    c. Evaluate immune response duration

2. Evaluate humoral and cellular immune response to administration of INO-3112 in subjects after chemoradiation therapy:
    - Evaluate immune response duration

Exploratory:

1. Explore anti-tumor response
2. Explore progression free survival

Sample Size:

A minimal of 20, and no more than 25 subjects will be enrolled in this study.

Study Design:
This will be a prospective, open-label, Phase I/IIa study of immunotherapy of INO-3112 in subjects with HPV-positive HNSCCa. Subjects will receive a course of treatment as described below and will be followed for safety as well as immune and clinical responses for 6 months from the last dose of immunotherapy.

The safety and effects of immunotherapy will be studied in following two populations:

1. In chemo- and radiation-naïve subjects who undergo definitive surgery and
2. In subjects after chemoradiation therapy

Doses of INO-3112 are based on safety experience in prior and on-going clinical trials. Based on the prior experience with these agents, dose escalation will not be conducted in this trial.

The study is divided into the following treatment cohorts:

I. INO-3112 (6 mg VGX-3100 + 1 mg INO-9012) will be given to subjects before and after definitive surgery

II. INO-3112 (6 mg VGX-3100 + 1 mg INO-9012) will be given to subjects after chemoradiation therapy

Cohort I: Immunotherapy will be given both before and after definitive surgery. Each subject will receive a total of 4 doses of treatment. Each treatment will be 6 mg of VGX-3100 and 1 mg INO-9012 (INO-3112) delivered IM followed by electroporation (EP). A minimum of 5 eligible subjects will be enrolled to this cohort.

Pre-Surgery:

1. Subjects will be enrolled if they have confirmed HPV-positive HNSCCa. Tumor tissue sample must be available to perform immunological correlates prior to definitive surgery.
2. After providing informed consent and being deemed eligible, subjects will receive immunotherapy. Up to 2 doses may be administered approximately once every 3 weeks (± 3 days) prior to definitive surgery.
3. The number of pre-surgery immunotherapies (one vs. two injections) will be based on the estimated time interval between pre-surgery evaluation and definitive surgery. Time to surgery according to standard practice is usually 2- 4 weeks; however, this varies due to ordinary logistical considerations independent of a clinical trial.
4. Surgery will not be delayed to allow for immunotherapy.

Post-Surgery:

1. Subjects will be seen approximately 2 weeks (± 7 days) post-surgery for follow up.
2. Subjects will undergo visual inspection to document healing by surgeon approximately 4 weeks post-surgery.
3. Post-surgery immunotherapy will proceed only after approval of the surgeon.

Post-Surgery (conti.):

4. Subjects will receive up to 3 doses given 3 weeks (± 3 days) apart. A total of 4 doses (pre- and post- surgery) will be administered.
5. Immunotherapy will be administered prior to adjuvant chemotherapy and/or radiation that may be indicated.
6. Adjuvant therapy will not be delayed due to immunotherapy.
7. Subjects will be followed for tumor status as per institutional standard of care.

Cohort II: Immunotherapy will start approximately 2-6 months after completion of definitive or adjuvant chemoradiation therapy in order to allow recovery from the treatment side effects of chemoradiation. INO-3112 will be delivered by IM injection followed by EP approximately once every 3 weeks for a total of 4 doses. A minimum of 10 eligible subjects will be enrolled into this cohort.

1. Subjects will be enrolled if they have HPV-16 and/or HPV-18 positive HNSCCa, and have completed chemoradiation therapy. Adequate tissue must be available to perform immunological correlates studies. Confirmation of HPV-16 and/or HPV-18 positivity is required prior to first dose of immunotherapy.
2. Subjects will be followed for tumor status as per normal institutional standard of care.

Study Endpoints:

Primary Endpoints: Safety and tolerability based on standard laboratory and clinical adverse event monitoring.

1. Adverse events will be measured and graded according to "Common Terminology Criteria for Adverse Events (CTCAE)", NCI version 4.03 issued by the US Department of Health and Human Services.
2. Frequency and severity of injection site reactions including administration site pain, skin erythema, induration, bleeding tenderness and infection.

Secondary Endpoints: Immune response after immunotherapy based on correlative measures.

1. Measure HPV-16 and HPV-18 specific antibody levels.
2. Using Antigen-specific IFN-γ ELISpot assays, determine the number of antigen-specific spot forming units (SFU) in response to stimulation with HPV-16 and HPV-18.
3. Evaluate cytotoxic T cells in response to HPV specific immunotherapy by flow cytometry.
4. Evaluate tumor infiltrating lymphocytes (TILs) by Immunohistochemistry (IHC) on pre-surgical and surgical samples.
5. Evaluate phenotypes of cultured TILs.

Exploratory Endpoints: Clinical response criteria as determined by:

1. Any evidence of anti-tumor response as assessed by the Investigator
2. Progression free survival

Study Population:

Inclusion Criteria

1. Signed and dated written Ethics Committee approved informed consent.
2. Age ≥18 years.
3. Histologically confirmed HPV-positive mucosal squamous cell head and neck cancer. Tumor tissue samples and the HPV test results must be available prior to first dose of Study Treatment:
    - For pre-surgical subjects, p16 positivity must be confirmed prior to first dose
    - For subjects post chemoradiation therapy, HPV-16 and/or HPV-18 positivity (as assessed by p16 IHC AND oncogenic HPV ISH or PCR) must be confirmed prior to first dose.
4. Adequate bone marrow, hepatic, and renal function. ANC (Absolute Neutrophil Count) ≥ $1.5x10^9$ cell/ml, platelets ≥75,000 /mm^3, hemoglobin ≥9.0 g/dL, total serum bilirubin within 1.5 x upper limit of normal (ULN), AST, ALT, CPK within 2.5 x ULN and performed within 4 weeks prior to the first administration of Study Treatment.
5. ECG with no clinically significant findings as assessed by the investigator.
6. No history of clinically significant autoimmune disease, HIV infection or other immunosuppressive disease.
7. ECOG (Eastern Cooperative Oncology Group) performance status of 0-1.
8. Women of childbearing potential must have a negative serum pregnancy test and agree to remain sexually abstinent, have a partner who is sterile (i.e., vasectomy), or use two medically effective methods of contraception (e.g. oral contraception, barrier methods, spermicide, intrauterine device (IUD)). Males with reproductive potential must be willing to use a condom and have their female sexual partners use another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant or a tubal ligation if the female partner could become pregnant. This requirement should be followed from screening through 24 weeks after last dose of immunotherapy.
9. Able and willing to comply with all study procedures.

Study Population: (continued):

Exclusion Criteria

1. Pregnant or breast-feeding subjects.
2. Anticipated concomitant immunosuppressive therapy (excluding non-systemic inhaled, topical skin and/or eye drop-containing corticosteroids).
3. Any concurrent condition requiring the continued use of systemic steroids (>10 mg prednisone or equivalent per day) or the use of immunosuppressive agents. All other corticosteroids must be discontinued at least 4 weeks prior first dose of study treatment.
4. Known history of hepatitis B or C with active viral replication.
5. Administration of any vaccine within 6 weeks of first dose of study treatment.
6. Tattoos, scars, or active lesions/rashes within 2 cm of the intended site of injection or if there is implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body.
7. Participation in another interventional clinical trial within 30 days before receiving first dose of study treatment. However, the subject may participate in observational studies.
8. Any cardiac pre-excitation syndromes, e.g. Wolff-Parkinson-White syndrome.
9. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
10. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness must not be enrolled into this study.
11. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.
12. Any other conditions judged by the investigator that would limit the evaluation of a subject.

Table S1: Cohort I Schedule of Events

Pre-surgery (Up to 2 doses of immunotherapy 3 weeks apart ± 3 days)
Post-surgery (Up to 3 doses of immunotherapy, 3 weeks apart; ± 3 days).
Subjects will receive no more than 4 doses of Immunotherapy (to include both pre and post-surgery dosing).

	Screening[1]	Pre Dose	Post Dose	Surgery	2 wk Post surgery	Inspection Visit[2]	2 wk f/u post last dose	LTFU/ EOS[3]
Procedures								
Informed Consent	X							
Medical History	X							
Physical Exam[4]/Assessment	X	X			X	X	X	X
Performance Status (ECOG)	X	X			X	X	X	X
Concomitant Medications	X	X			X	X	X	X
Adverse Events	X	X	X		X	X	X	X
Injection site assessment			X[5]				X	
Wound healing Inspection						X		
Tumor evaluation	X							
Clinical Labs								
CBC w diff (4ml)	X	X[6]					X	X
Chemistry (5ml)[7]	X	X[6]					X	X
PT-INR/PTT (4ml)	X							
B-hCG (1ml)[8]	X	X						
Viral Serology (5ml)[9]	X							
CPK (1ml)	X						X	
Other Clinical Procedures								
ECG 12-lead	X							
Research Immunology								
Serum and Whole Blood (1 Red Top and 4 ACD tube)[10]	X	X		X	X	X	X	X
Tissue Sample[11]	X			X				
HLA Testing (no action required)		X[12]						
IMMUNOTHERAPY		X						
Download EP Data			X					
Patient Reminder Card			X					

1- Screening to be done within 28 days prior to first dose. If a subject is rescreened, the screening clinical labs and 12-lead ECG must be repeated unless they will occur within 4 weeks of the subject's first dose. All other screening procedures do not need to be repeated.
2- Inspection visit occurs 4 weeks post-surgery (± 7 days)
3- LTFU: Long term follow up: every 3 months (±7 days) for 6 months from the last dose of immunotherapy, End of Study (EOS) defined as last LTFU visit
4- Includes weight, vital signs, oxygen saturation (height will be collected as part of Screening visit). Assessment includes

medical/clinical assessment
5- To be done 30-45 minutes post dose
6- If clinical screening labs (CBC and Chemistry) were performed within 72 hours prior the subject's first dose, these labs are not required to be redrawn prior to the subject's first dose
7- Total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin.
8- Women of childbearing potential. Serum β-hCG at screening and Urine β-hCG within 72 hours of each dose.
9- Antibody to human immunodeficiency virus (HIV-Ab), Hepatitis B surface antigen (HBsAg), antibody to Hepatitis C virus (HCV)
10- At least 34 mL (4 x 8.5 mL ACD tubes) whole blood and 4 mL serum per time point to be collected. A total of at least 68 mL whole blood and 4 mL serum should be collected prior dosing on Day 0.
11- Paraffin-embedded tumor tissue or unstained slides for IHC and ISH. Fresh cut primary tumor tissue at the time of surgery.
12- To be performed using available PBMC from whole blood immunology sample.

Table S2: Cohort II Schedule of Events

Immunotherapy starts ~2-6 months post chemoradiation. Doses are q3 weeks (± 3 days).

	Screening[1]	Pre Dose	Post Dose	2 wk f/u post last dose	LTFU/EOS[2]
Procedures					
Informed Consent	X				
Medical History	X				
Physical Exam[3]/Assessment	X	X		X	X
Performance Status (ECOG)	X	X		X	X
Concomitant Medications	X	X		X	X
Adverse Events	X	X	X	X	X
Injection site assessment			X[4]		
Clinical Labs					
CBC w diff (4ml)	X	X[5]		X	X
Chemistry (5ml)[6]	X	X[5]		X	X
PT-INR/PTT (4ml)	X				
B-hCG (1ml)[7]	X	X			
Viral Serology (5ml)[8]	X				
CPK (1ml)	X			X	
Other Clinical Procedures					
ECG 12-lead	X				
Research Immunology					
Serum and Whole Blood (1 Red Top and 4 ACD tube)[9]	X	X		X	X
Tissue Sample[10]	X				
HLA Testing *(no action required)*		X[11]			
IMMUNOTHERAPY		X			
Download EP Data			X		
Patient Reminder Card			X		

1- Screening to be done within 28 days prior to first dose. If a subject is rescreened, the screening clinical labs and 12-lead ECG must be repeated unless they occur within 4 weeks of the subject's first dose. All other screening procedures do not need to be repeated.
2- LTFU: Long term follow up: every 3 months (±7 days) for 6 months from the last dose of immunotherapy, End of Study (EOS) defined as last LTFU visit
3- Includes weight, vital signs, oxygen saturation
4- To be done 30-45 minutes post dose
5- If clinical screening labs (CBC and Chemistry) were performed within 72 hours prior the subject's first vaccination, these labs are not required to be redrawn prior to the subject's first dose
6- Total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin.
7- Women of childbearing potential only. Serum β-hCG at screening and Urine β-hCG within 72 hours of each dose

8- HIV, Hepatitis BsAg, Hepatitis C
9- At least 34 mL (4 x 8.5 mL tubes) whole blood and 4 mL serum per time point to be collected. A total of at least 68 mL whole blood and 4 mL serum should be collected prior to dosing on Day 0.
10- Paraffin-embedded tumor tissue or unstained slides for IHC and ISH. Confirmation of HPV-16 and/or HPV-18 positivity prior to first dose.
11- To be performed using available PBMC from whole blood immunology sample.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

1.1.1 HPV related squamous cell carcinoma of the head and neck

Squamous cell carcinoma of the head and neck (HNSCC) is diagnosed in over 500,000 patients worldwide each year, accounting for 5% of all malignancies [1]. A significant subset of HNSCCa is now known to be caused by oncogenic human papilloma virus (HPV) infection. HPV-associated SCCa arises predominantly in the oropharynx and occurs in patients (strong male predominance) without a strong tobacco and/or alcohol consumption history. In a retrospective study, tumor tissues from 253 patients with newly diagnosed or recurrent HNSCCa were tested for the presence of HPV genome by use of polymerase chain reaction (PCR)-based assays, Southern blot hybridization, and in situ hybridization (ISH). The viral E6 coding region was sequenced to confirm the presence of tumor-specific viral isolates. HPV was detected in 62 (25%) of 253 cases. High risk, tumorigenic type HPV16 was identified in 90% of the HPV-positive tumors. HPV-16 was localized specifically by ISH within the nuclei of cancer cells in pre-invasive, invasive, and lymph node disease. Southern blot hybridization patterns were consistent with viral integration. Poor tumor grade and oropharyngeal site independently increased the probability of HPV presence [2].

The molecular and clinical profiles of HPV positive tumors are distinct from those of HPV negative cancers. In the typical HPV negative squamous cell carcinomas, p53 mutations are frequent along with decreased p16 and increased levels of pRb [3]. By contrast, HPV positive carcinomas are associated with wild type (albeit dysregulated) p53, down regulation of pRb, and up-regulation of p16, the latter serving as a surrogate marker for the disease itself. As compared with HPV-negative oropharyngeal cancers, HPV positive oropharyngeal cancers are less likely to occur among moderate to heavy drinkers and smokers, have characteristic basaloid morphology, and have improved disease-specific survival [2].

The HPV viral oncoproteins, E6 and E7, are predominantly responsible for oncogenesis. Like many viral oncoproteins, E6 and E7 are expressed early in the course of infection and have multifunctional roles. E6 promotes degradation of p53, indirectly activates telomerase, and disrupts the function of the cellular phosphatase tumor suppressor PTPN13. E7 inactivates pRb and activates Mi2beta. Together, these oncogenic alterations drive rapid cellular proliferation, suppress or downregulate key tumor suppressor proteins, and lead to cellular immortality. In addition, E6/E7 expression is vital for malignancy and is required to maintain a malignant transformed phenotype [4]. It has been shown that persistence of malignant cells requires the continuous expression of the human papillomavirus type 16 oncogenes [5].

Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. HPV related tumors are generally more responsive to chemotherapy and radiation compared to non-HPV related HNSCCa [6]. In a landmark retrospective analysis of RTOG0129, Ang *et al.* described that patients with HPV related tumors had superior 3-year rates of overall survival compared to non-HPV related tumors. After adjusting for age, race, tumor and

nodal stage, tobacco exposure, and treatment assignment, patient with HPV-related HNSCCa had a 58% reduction in the risk of death (hazard ratio, 0.42; 95% CI, 0.27 to 0.66). Smoking history had a significant impact on survival in this otherwise favorable prognosis population; the risk of death increased significantly with each additional pack-year of tobacco smoking [6].

Despite the availability of highly curative treatments, at least 10-30% of patients with HPV related HNSCCa (depending on smoking status and other unknown variables) will eventually develop locally recurrent and/or metastatic disease. The prognosis of patients with locally recurrent or metastatic HNSCCa is dismal, and palliative treatment options remain extremely limited. A few patients with recurrent disease are candidates for salvage therapies, including potentially curative surgery [7]. Highly selected patients in this setting may benefit from re-irradiation although the morbidity of this approach is substantial [8]. Palliative systemic therapy remains the mainstay for most patients. Despite the availability of cytotoxic chemotherapy and targeted agents like cetuximab, median survival for patients with incurable HNSCCa is around 10.5 months [9].

1.1.2 Rationale for HPV specific immunotherapy with a therapeutic HPV vaccine

Current treatment of HPV related HNSCC could potentially be improved with addition of immunotherapy. Commercially available preventive HPV vaccines generate neutralizing antibodies against HPV major capsid protein L1, but they do not exert therapeutic effects on existing lesions and are unlikely to have an effect on HPV associated malignancy because they do not engender a cytolytic T-cell response [10]. HPV specific immunotherapy, on the other hand, may eliminate preexisting lesions and infections by generating cellular immunity against HPV infected cells. HPV E6 and E7 oncoproteins represent ideal targets for therapeutic intervention because of their constitutive expression in HPV associated tumors and their crucial role in the induction and maintenance of HPV associated disease [10].

One therapeutic approach is to modify the virus itself and use it as an immunogen. In a recent study, Wieking *et al.* described the generation of a mutant non-oncogenic HPV16 E6D/E7D construct. This construct, expressed either as a stable integrant or in the [E1-, E2b-] adenovirus, lacks the ability to transform human cells but retains the ability to induce an HPV-specific immune response. In a mouse model, vaccination with Ad5 [E1-, E2b-]-E6D/E7D in immune competent mice enhanced immune related clearance *in vivo* during standard therapy for HPV related cancer with cisplatin and radiation [11].

1.1.3 Rationale for immunotherapy with synthetic DNA delivered by electroporation

The delivery of synthetic DNA using electroporation represents another approach that offers several potential advantages. Synthetic DNA in the form of a plasmid are not known to elicit anti-vector immune responses, providing the capacity for repeated administrations that may be required to achieve and maintain effective immune responses. Furthermore, the plasmids can be engineered to express a variety of HPV related antigenic peptides and/or proteins [10].

Inovio has developed a novel immunotherapeutic from synthetic HPV-16/18 E6 and E7 DNA sequences. Phase 1 clinical results with VGX-3100 delivered by *in vivo* electroporation (EP) were recently published [12]. Eighteen women previously treated for cervical intraepithelial neoplasia (CIN) grade 2 or 3 were treated with a three-dose (intramuscular) regimen of a highly engineered DNA (VGX-3100) in a dose escalation study (0.3, 1, and 3 mg per plasmid). HPV specific CD8+ T cells were shown to exhibit full cytolytic functionality in all cohorts. VGX-3100 was shown to drive robust immune responses to E6 and E7 from high-risk HPV serotypes and could thereby

contribute to elimination of HPV infected cells and subsequent regression of the HPV induced dysplastic process [12].

Because E6 and E7 are responsible for the transformation of cancer cells and are required for maintenance of HPV associated HNSCC, we hypothesize that generation of robust T-cell immunity to E6 or E7 will lead to down-regulation of cancer survival pathways and disease stabilization or regression.

1.1.4 Rationale for addition of IL-12 plasmid DNA molecular adjuvant

DNA vaccines primarily elicit $CD4^+$ T-cell responses in humans, and there has been interest in discovering ways to boost the immune response post vaccination. In addition to electroporation, Inovio has also shown that IL-12 DNA can be used as a molecular adjuvant to enhance immune responses. This is done by co-delivering DNA plasmids expressing immune modulators. The IL-12 DNA adjuvant is a dual promoter expression plasmid expressing the genes encoding human IL-12 proteins p35 and p40 under separate regulatory control.

In a clinical study with a similarly designed HIV DNA immunogen, co-administration of IL-12 DNA with DNA encoding antigenic proteins was associated with an enhanced CD8 vaccine immune response [13, 14]. The use of IL-12 DNA was associated with expansion of antigen-specific IFN-γ positive effector cells as well as granzyme B production. The immunity induced included both a CD8 as well a CD4 component [15, 16]. The evaluation of recombinant IL-12 DNA has yielded a wealth of safety information to date in humans and forms the preliminary basis for the predicted safety profile for the use of IL-12 plasmid as an adjuvant component of the vaccine in the proposed clinical study.

1.1.5 Rationale for electroporation (EP) with CELLECTRA® device

The use of EP with the CELLECTRA® device has been shown to increase the expression of VGX-3100. EP is the use of transmembrane electric field pulse to induce microscopic pathways (pores) in a bio-membrane. The electric field allows macromolecules, ions, and water to pass from one side of the membrane to the other. The presence of a constant field influences the kinetics of directional translocation of the macromolecular plasmid, such that the plasmid delivery *in vivo* has been sufficient to achieve physiological levels of secreted proteins. Intramuscular injection of plasmid followed by EP has been used very successfully to deliver therapeutic genes that encode for a variety of hormones, cytokines or enzymes in a variety of species [17]. The design of software that enables constant current EP to deliver plasmids allows for the individual resistance of the treated muscle to be taken into consideration and yields highly efficient *in vivo* plasmid expression [18].

Ten healthy adults were electroporated using CELLECTRA®, to evaluate the pain following EP in 10 healthy subjects, was evaluated immediately after, and at 5, 15, 30 minutes and 1 hour after the procedure. Subjects used a Visual Analog Scale (VAS) questionnaire, 10 cm in length, anchored by word descriptors at each end, “No Pain” and “Worst Pain”, to mark their pain related to the treatment. Subjects reported a mean (±sem) score of 6.3 (±0.7) immediately after treatment and 2.8 (±0.5) approximately 5 minutes after the procedure [19]. These data show that the pain associated with electroporation is acute and diminishes quickly. Therefore, the risk to subjects is minimal, and benefit outweighs the risk.

In this proof of concept study, we propose to evaluate the safety and immune effects of the immunotherapy with VGX-3100, synthetic plasmid DNA encoding HPV-16 and HPV-18 E6/E7 antigens co-administered with a recombinant IL-12 molecular adjuvant (INO-9012).

1.2 Investigational Agents

1.2.1 VGX-3100 (Common Name)

Chemical Name: Circular, double stranded, deoxyribonucleic acid consisting of 3782 base pairs for the pGX3001 plasmid and 3824 base pairs for the pGX3002 plasmid.

Distinguishing Name: Eukaryotic expression plasmids containing HPV-16 and -18 E6 & E7-encoding transcription unit controlled by a synthetic, CMV promoter, and elements required for replication and selection in *E. coli*, namely a pUC origin of replication (pUC Ori) and a kanamycin resistance gene (Kan R).

1.2.2 INO-9012 (Common Name)

Chemical Name: Circular, double stranded, deoxyribonucleic acid consisting of 6259 base pairs for the pGX6001 (also called IL-12 DNA) plasmid.

Distinguishing Name: Eukaryotic expression plasmids containing synthetic IL-12 p35 light chain and p40 heavy chain (pGX6001) controlled by a dual promoter vector, a bGH poly A tract, bacterial origin of replication to support production of the plasmid in *E. coli*, and a kanamycin resistance gene (Kan R).

VGX-3100 and INO-9012 combination is referred to as INO-3112 in this protocol.

1.2.3 CELLECTRA®5P device for intramuscular electroporation

The CELLECTRA®5P device is a portable, battery powered medical device designed to generate a minimally controlled electric field which temporarily and reversibly increases cellular membrane permeability without damaging the tissue. During the period of increased permeability, an injected plasmid DNA formulation can be injected into the cells. Additional information on the investigational device is available in the manual.

1.3 Preclinical Data

1.3.1 VGX-3100 Preclinical Data

DNA plasmids for HPV-16 (pCon16E6E7) and HPV-18 (pCon18E6E7) have been studied for pre-clinical expression and immunogenicity. Preclinical GLP toxicology and biodistribution studies with VGX-3100 have demonstrated an acceptable safety profile in New Zealand white rabbits (Refer to INO-3112 IB for details).

1.3.2 INO-9012 Preclinical Data

IL-12, a dendritic cell (DC)-produced cytokine, is a strong stimulator of NK cells as well as of T lymphocyte activity. IL-12 supports the differentiation of antigen specific CD4 T cells to produce Th1 cytokines including IFN-gamma and triggers the expansion of antigen specific CD8 T cells to express cytotoxic mediators, such as granzyme B/perforin [20-23]. The use of IL-12 DNA (e.g. INO-9012) as an immune adjuvant has proven effective at improving immune priming *ex vivo* as well as in animal models [24-26]. See Section 4 of the INO-3112 IB for details.

1.4 Clinical Data

1.4.1 VGX-3100 Clinical Data

VGX-3100 has been tested in 2 Phase I clinical trials (HPV-001 and HPV-002) in adult females post-surgical or ablative treatment of grade 2 or 3 cervical intraepithelial neoplasia (CIN) to evaluate safety and immunogenicity [12]. Safety data showed only mild to moderate Grade 1 and 2 adverse events, mainly injection site local reactions and non-clinically significant laboratory abnormalities. There were no serious adverse events attributed to treatment in any of the subjects enrolled and no study subjects discontinued early.

VGX-3100 is being evaluated in an ongoing Phase II study in women with high grade CIN (HPV-003). VGX-3100 was immunogenic and efficacious against CIN 2/3 without any significant safety concerns (Refer to INO-3112 IB for details).

1.4.2 INO-9012 Clinical Data

The safety profile associated with IM administration of IL-12 plasmid DNA alone or followed by EP has been acceptable in previous clinical studies. Clinical results from three different studies substantiate the safety and tolerability profile of IL-12 plasmid DNA. IL-12 plasmid DNA has been used in several cohorts in the following four phase I clinical protocols.

Protocol #	Co-administered with	# subjects received IL-12 DNA
HVTN-060	HIV-1 gag p37	80
HVTN-063	HIV-1 gag p37	30
HVTN-070	PENNVAX®-B (gag, pol, env)	30
HVTN-080	PENNVAX®-B (gag, pol, env)	30

IL-12 DNA was delivered without EP in HVTN-060, -063 and -070 but was followed by EP in HVTN-080. In the protocol HVTN-080, PENNVAX®-B or placebo were delivered via IM injection followed by electroporation with the CELLECTRA®-5P device in 48 healthy volunteers. The regimen consisted of 3 mg of PENNVAX®-B with or without plasmid encoding IL-12 at months 0, 1 and 3. This study established that a highly engineered DNA vaccine delivered intramuscularly followed by EP can induce frequent and robust T-cell responses in humans.

In summary of above clinical studies, no pattern of systemic AEs emerged, and no SAEs related to the study products were observed. The plasmid DNA vaccine co-administered with IL-12 plasmid DNA as a cytokine adjuvant were well-tolerated (Refer to INO-3112 IB for details).

1.4.3 CELLECTRA® Device Clinical Use

Clinical Experience with Inovio Plasmid DNA-based Immunotherapy Delivered by Electroporation using CELLECTRA® device:

The underlying basis for all studies of plasmid DNA vaccines is the fairly substantial safety database that exists for the varied plasmid DNA vaccine candidates that have now been studied in humans. The plasmid DNA platform has been utilized for vaccine candidates for a variety of

disease indications and infectious agents (e.g., HIV, HPV, Influenza, SARS, West Nile virus, Ebola among others) in addition to plasmid cytokine adjuvants such as IL-2, IL-12 and IL-15.

Four separate GLP toxicology and biodistribution studies have been performed for eight additional plasmid DNA vaccine candidates developed by Inovio Pharmaceuticals, Inc. with identical backbones delivered by electroporation yielding similar toxicity and biodistribution profiles.

As of April 7, 2015, 587 human subjects had been treated with electroporation using the Inovio CELLECTRA® device in more than 14 different studies. The total includes more than 1300 injections (IM or ID) of DNA followed by EP and approximately 186 injections of placebo followed by EP (refer to Investigator Brochure for details) without any clinically significant safety issues.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Dose Rationale

The doses selected are based on previous human experience and preclinical data with VGX-3100 and other DNA vaccines. A total dose of 6 mg VGX-3100 DNA has been selected for this study based on the safety and immunogenicity data generated in the HPV-001 study, where 6 mg of DNA were delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses in the high dose cohort compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 1.1) without significant safety issues [12].

This dose-trend was consistent with prior expectations, suggesting that it may be a real effect rather than random variation. Adverse events from previous human studies with closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure. No unexpected or severe adverse events were observed in any of the 3 dose cohorts.

Table 1.1: Percent of subjects responding and average SFU/10^6 PBMC in responders for each antigen by cohort in Protocol HPV-001 Interferon-γ ELISpot

Cohort	Low (0.6 mg)		Mid (2 mg)		High (6 mg)	
Antigen	**%RR**	**AVG**	**%RR**	**AVG**	**%RR**	**AVG**
16E6	33%	107	50%	243	50%	1341
16E7	17%	198	50%	104	67%	143
18E6	50%	359	50%	338	83%	664
18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

RR = Response Rate

The IL-12 plasmid dose is based on previous experience in the HVTN 080 study, where 1 mg of IL-12 plasmid was co-administered with PENNVAX®-B followed by EP. HIV-specific $CD4^+$ T cell responses were generated in 67.9% (19/28) of PENNVAX®-B + IL-12 recipients after two vaccinations, compared to 30.0% (3/10) with PENNVAX®-B alone. Co-administration with IL-12 resulted in $CD4^+$ T cell responses in ~81% vs. 44% without IL-12 after three doses. Delivery of PENNVAX®-B via EP increased the frequency of $CD8^+$ T cell responses even more dramatically. $CD8^+$ responses were detected in 33% of PENNVAX®-B and 52% of PENNVAX®-B + IL-12 recipients after 3 vaccinations. Six months after the third vaccination 43% of individuals were still

able to respond to HIV peptide pools. Overall, 71% of individuals vaccinated with PENNVAX®-B + IL-12 plasmid followed by EP developed either a $CD4^+$ or $CD8^+$ T-cell response after the second vaccination and 89% developed $CD4^+$ or $CD8^+$ T-cell responses after the third vaccination. As noted above the addition of the IL-12 plasmid to the vaccine did not alter the safety profile. We do not anticipate any significant risks with the administration of this dose.

1.5.2 Risks/Benefit Assessment

In accordance with the International Conference on Harmonisation (ICH), this study has been designed to minimize risk to study subjects. Potential risks of study products and administration from studies using similar plasmids with the identical DNA backbone are listed in Table 1.2.

The potential side effects of treatment with the investigational products may include discomfort related to the electroporation technique such as local edema, swelling, or pain. Systemic side effects with vaccines based on the identical SynCon® backbone have been demonstrated to be generally safe in more than 580 subjects (data as of May 15, 2015). The potential benefit of this study is to determine whether this immunotherapy will generate protective levels of antibodies and cytotoxic T-cells as treatment for those with HPV associated HNSCCa.

Table 1.2: Summary of Reported Adverse Events from previous clinical trials and Potential Risks of DNA based immunotherapy delivered IM+EP with CELLECTRA®

Common	• Mild to moderate administration site pain, erythema, tenderness, swelling, induration • Malaise/fatigue, myalgia, or headache in the first few days following injection
Less common	• Injection site hematoma, bruising/ecchymosis, laceration, other transient lesions, or bleeding related to the injection procedure • Arthralgia or nausea
Uncommon or rare	• Severe administration site pain or tenderness • Rash following injection/EP • Vasovagal reaction/lightheadedness/dizziness related to the injection/EP procedure • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Muscle damage at the administration site • Autoimmune disease • Electrical injury • Disruption of function of implanted electronic medical devices • Exacerbation of cardiac arrhythmia • Effects on the fetus and on pregnancy

2 Study Objectives

2.1 Primary Objectives

Evaluate safety of treatment with INO-3112.

2.2 Secondary Objectives

1. Evaluate humoral and cellular immune response to administration of INO-3112 in chemo- and radiation-naïve subjects who undergo definitive surgery:
    a. Pre- and Post-immunotherapy tissue analysis to evaluate infiltration of T cells in the tumor.
    b. Evaluate effect of number of doses on immune responses.
    c. Evaluate immune response duration.

2. Evaluate humoral and cellular immune response to administration of INO-3112 in subjects after chemoradiation therapy:
    - Evaluate immune response duration.

2.3 Exploratory Objectives

1. Explore anti-tumor response
2. Explore progression free survival

3 Study Design

This will be a prospective, open-label, Phase I/IIa study of immunotherapy with INO-3112 in subjects with HPV-positive HNSCCa. Subjects will receive a course of treatment as described below and will be followed for safety as well as immune and clinical responses for 6 months from the last dose of immunotherapy.

The safety and effects of immunotherapy will be studied in two populations:

1. In chemo- and radiation-naïve subjects who undergo definitive surgery and
2. In subjects after chemoradiation therapy.

Doses of INO-3112 are based on safety experience in prior and on-going clinical trials. Based on the prior experience with these agents, dose escalation will not be conducted in this trial.
The study is divided into the following treatment cohorts:

I. INO-3112 (6 mg VGX-3100 + 1 mg INO-9012) will be given to subjects before and after definitive surgery.

II. INO-3112 (6mg VGX-3100 + 1 mg INO-9012) will be given to subjects after chemoradiation therapy.

3.1 General Design

Study Schema: Eligible subjects will receive highly engineered plasmid DNA encoding HPV-16 and HPV-18-E6 & E7 transcription unit antigens (VGX-3100) combined with the DNA encoding IL-12 (INO-9012) followed by EP with the CELLECTRA®5P device.

COHORT I: Immunotherapy will be given both before and after definitive surgery. Each subject will receive a total of 4 doses of treatment, 1-2 of them pre-surgery. Each treatment will be 6 mg

of VGX-3100 and 1 mg INO-9012 (INO-3112) delivered IM followed by EP. A minimum of 5 eligible subjects will be enrolled to this cohort.

Pre-Surgery:

1) Subjects will be enrolled if they have confirmed HPV positive mucosal HNSCCa. Tumor tissue samples must be available to perform immunological correlates prior to definitive surgery.
2) After providing informed consent and being deemed eligible, subjects will receive immunotherapy. Up to 2 doses may be administered approximately once every 3 weeks (±3 days) prior to definitive surgery.
3) The number of pre-surgery immunotherapies (one vs. two injections) will be based on the estimated time interval between pre-surgery evaluation and definitive surgery. Time to surgery according to standard practice is usually 2- 4 weeks; however, this varies due to ordinary logistical considerations independent of a clinical trial.
4) Surgery will not be delayed to allow for immunotherapy.

Post-Surgery:

1) Subjects will be seen approximately 2 weeks (±7 days) post-surgery for follow up.
2) Subjects will undergo visual inspection to document healing by surgeon approximately 4 weeks post-surgery.
3) Post-surgery immunotherapy will proceed only after approval of the surgeon.
4) Subjects will receive up to 3 doses given 3 weeks (±3 days) apart. A total of 4 doses (pre- and post-surgery) will be administered.
5) Immunotherapy will be administered prior to adjuvant chemotherapy and/or radiation that may be indicated.
6) Adjuvant therapy will not be delayed for immunotherapy.
7) Subjects will be followed for tumor status as per institutional standard of care.

COHORT II: Immunotherapy will start approximately 2-6 months after completion of definitive or adjuvant chemoradiation therapy in order to allow recovery from the treatment side effects of chemoradiation. INO-3112 (6 mg of VGX-3100 and 1 mg INO-9012) will be delivered by IM injection with EP once every 3 weeks (±3 days) for a total of 4 doses. A minimum of 10 subjects will be enrolled into this cohort.

1) Subjects will be enrolled if they have HPV-16 and/or HPV-18 positive HNSCCa confirmed by ISH or PCR, and have completed chemoradiation therapy. Adequate tissue must be available to perform immunological correlates studies. Confirmation of HPV-16 and/or HPV-18 positivity is required prior to first dose of immunotherapy.
2) Subjects will be followed for tumor status as per normal institutional standard of care.

Sample Size: A minimal of 20 but no more than 25 eligible subjects will be enrolled in this study.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary study endpoint is safety and tolerability based on standard laboratory and clinical adverse event monitoring:

1. Adverse events will be measured and graded according to "Common Terminology Criteria for Adverse Events (CTCAE)", NCI version 4.03 issued by the US Department of Health and Human Services.
2. Frequency and severity of injection site reactions including administration site pain, skin erythema, induration, bleeding, tenderness and infection.

3.2.2 Secondary Endpoint

The secondary endpoints is immune response after immunotherapy based on correlative measures:

1. Measure HPV-16 and HPV-18 specific antibody levels. A standardized binding ELISA will be performed to measure the anti–HPV16/18 E6 or E7 antibody response induced by VGX-3100 and INO-9012. 96-well enzyme immunoassay plates will be coated with HPV16 or HPV18 E6 or E7 proteins (1 μg/ml) (recombinant HPV16/18 E7 and HPV16 E6 procured from ProteinX Lab, HPV18 E6 from Impact Biologicals). Subject sera will be diluted with 1% bovine serum albumin in PBS and tested in triplicate with an automated and calibrated plate washer and read on a kinetic microplate reader (Molecular Devices). Samples will be scored as positive if the average optical density (OD) was greater than 0.15 absorbance units and greater than the average OD before preimmunization plus 2.5 times the standard deviation of the OD compared to corresponding preimmunized samples at the same dilution.

2. Using Antigen-specific IFN-γ ELISpot assays, determine the number of antigen-specific spot forming units (SFU) in response to stimulation with HPV16 and HPV18. T cell responses will be assessed using an HPV IFN-γ ELISpot assay. PBMCs will be thawed and plated at 200,000 cells/well. Cells will be incubated with HPV16 and HPV18 peptides corresponding to E6 and E7 proteins of HPV. The three sets of peptides, each contain 15–amino acid residues overlapping by 8 amino acids representing the entire consensus E6/E7 fusion protein sequence of HPV16 or HPV18, and are pooled at a concentration of 2 μg/ml per peptide into two pools [12]. After an overnight incubation, IFN-gamma release will be detected using standard procedures. The average number of SFU counted in R10 wells will be subtracted from the average in individual HPV peptide wells and then adjusted to 1×10^6 PBMCs for each HPV peptide pool. Additionally, PBMC responses against a pool of known antigenic epitopes combined from Cytomegalovirus, Epstein Barr Virus and Influenza (CEF) will be tested in order to track general cellular immune competence during the study in the same manner as HPV responses described above.

3. Evaluate cytotoxic T cells in response to HPV specific immunotherapy by flow cytometry. Additional assessment of cellular immune activity will occur via the application Flow Cytometry. Flow Cytometric assays will include an examination the influence of immunotherapy on the ability of patient T cells to exhibit phenotypic markers associated

with cytolytic potential after short-term stimulation by HPV E6 and E7 of VGX-3100 antigen (hereafter referred to as "CTL Phenotyping"), the ability of patient T cells to remain active in the presence of long-term antigen exposure and efficiently synthesize proteins used in lytic activity (hereafter referred to as "Lytic Granule Loading") and the ability of patient T cells to effectively employ Granzyme B for the purposes of lytic degranulation and killing of target cells expressing HPV E6 and E7 (hereafter referred to as "Killing"). These panels may vary as newer information becomes available within the literature.

i. The assay for CTL Phenotyping will employ a 6-hour *in vitro* stimulation of unfractionated patient PBMCs using peptides spanning VGX-3100 antigens as described above, an irrelevant peptide control (OVA) and a positive control (Staphylococcal Enterotoxin B or a combination of phorbol 12-myristate 13-acetate and Ionomycin). The CTL Phenotyping assay will examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), CD45RO, CCR7 (memory subset identification), and CD107a. The CTL Phenotyping assay will additionally analyze the following intracellular markers: Interferon Gamma (Th1 biasing cytokine), Tumor Necrosis Factor Alpha, Granzyme A, Granzyme B and Perforin (proteins involved in lytic degranulation and cytotoxic potential). This panel of markers may vary as new information becomes available.

ii. The Lytic Granule Loading assay will employ a 120-hour *in vitro* stimulation of unfractionated patient PBMCs using peptides spanning VGX-3100 antigens, an irrelevant peptide control (OVA) and a positive control (Concanavalin A). The Lytic Granule Loading assay will examine the following external cellular markers: CD3, CD4, CD8 (T cell identification), and CD137 (also known as 41BB – marker of T cell activation). The Lytic Granule Loading assay will additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin and Perforin (proteins involved in lytic degranulation and cytotoxic potential). This panel of markers may vary as new information becomes available.

iii. The Killing assay will employ a 120-hour *in vitro* stimulation of unfractionated patient PBMCs using peptides spanning VGX-3100 antigens. Stimulated whole PBMCs or CD8+ T cells isolated after the 120-hour incubation will be co-incubated for 60 minutes with target cells that have received a membrane stain that differentiates them from patient PBMCs/CD8+ T cells and have additionally been pulsed with a reagent which is activated only when the cell is actively in apoptosis (programmed cell death). At the end of this time cells will be washed and target cells identified using the membrane stain and analyzed for the presence of the active substrate as a measure of functional cytolytic degranulation and killing Employment of this assay may change pending readouts from the Lytic Granule Loading assay. Description of previous use of these assays or variants thereof can be found in Bagarazzi *et al*. Immunotherapy against HPV16/18 [12]. The construction of this assay may vary as new information becomes available.

4. Evaluate tumor infiltrating lymphocytes (TIL) by Immunohistochemistry (IHC) on pre-surgical and surgical samples. HPV immunotherapy prior to surgery will provide us with a unique opportunity to determine if the VGX-3100 induced immune response can directly target the HPV positive tumor cells. Therefore, we will perform immunohistochemistry on

samples obtained prior to or at study entry as well as on samples that will be obtained from resection of the primary tumor in Cohort I.

5. Evaluate phenotypes of cultured TILs. In addition, for Cohort I we will use any remaining fresh (unfixed) tissue 1) isolate TILs and 2) isolate tumor cells to use for *in vitro* stimulation of lymphocytes isolated from the periphery. In order to determine if HPV E6 and E7 specific lymphocytes have migrated to the tumor we will isolate TILs by standard procedures from tumor pre- and post-immunotherapy. We will utilize Affymetrix/Panomics Luminex Plex System to define the immunological transcriptome. This gene analysis will incorporate analysis of Perforin, IFN-gamma, IL-2, IL-10 and IL-4 to account for antigen specific CD8 and CD4 T cells as well as Treg upregulation. In addition, confirmatory genes will be included. Such genes are transcription factors for these cell types; Tbet, GATA2, FOXP2 and RORC.

   Secondly, during digestion of the tumor with collagenase for lymphocytes we will save and cryopreserve tumor cells as well. These tumor cells can be used in *in vitro* assays to stimulate lymphocytes isolated from the periphery of the respective subject. We expect that we will observe an immune response to peptides. However, stimulation with tumor cells will provide information about lymphocytes ability to target the tumor cells.

3.2.3 Exploratory Endpoints: Clinical response criteria as determined by:

1. Any evidence of anti-tumor response as assessed by the Investigator
2. Progression free survival

4 Subject Selection and Withdrawal

Exceptions to eligibility will not be granted for this study.

4.1 Inclusion Criteria

1. Signed and dated written Ethics Committee approved informed consent.
2. Age ≥18 years.
3. Histologically confirmed HPV-positive mucosal squamous cell head and neck cancer. Tumor tissue samples and the HPV test results must be available prior to first dose of Study Treatment.
   - For pre-surgical subjects, p16 positivity must be confirmed prior to first dose
   - For subjects post chemoradiation therapy, HPV-16 and/or HPV-18 positivity (as assessed by p16 IHC AND oncogenic HPV ISH or PCR) must be confirmed prior to first dose.
4. Adequate bone marrow, hepatic, and renal function. ANC (Absolute Neutrophil Count) ≥ $1.5x10^9$ cell/ml, platelets ≥75,000 /mm^3, hemoglobin ≥ 9.0 g/dL, concentrations of total serum bilirubin within 1.5 x upper limit of normal (ULN), AST, ALT, CPK within 2.5 x ULN, and performed within 4 weeks prior to the first administration of Study Treatment.
5. ECG with no clinically significant findings as assessed by the investigator.
6. No history of clinically significant autoimmune disease, HIV infection or other immunosuppressive disease.
7. ECOG (Eastern Cooperative Oncology Group) performance status of 0-1.

8. Women of childbearing potential must have a negative serum pregnancy test and agree to remain sexually abstinent, have a partner who is sterile (i.e., vasectomy), or use two medically effective methods of contraception (e.g. oral contraception, barrier methods, spermicide, intrauterine device (IUD)). Males with reproductive potential must be willing to use a condom and have their female sexual partners use another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant or a tubal ligation if the female partner could become pregnant. This requirement should be followed from screening through 24 weeks after last dose of immunotherapy.
9. Able and willing to comply with all study procedures.

4.2 Exclusion Criteria

1. Pregnant or breast-feeding subjects.
2. Anticipated concomitant immunosuppressive therapy (excluding non-systemic inhaled, topical skin and/or eye drop-containing corticosteroids).
3. Any concurrent condition requiring the continued use of systemic steroids (>10 mg prednisone or equivalent per day, see above) or the use of immunosuppressive agents. All other corticosteroids must be discontinued at least 4 weeks prior to first dose of study treatment.
4. Known history of hepatitis B or C with active viral replication.
5. Administration of any vaccine within 6 weeks of first dose of study treatment.
6. Tattoos, scars, or active lesions/rashes within 2 cm of the intended site of injection or if there is implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body.
7. Participation in another interventional clinical trial within 30 days before receiving first dose of study treatment. However, the subject may participate in an observational studies.
8. Any cardiac pre-excitation syndromes, e.g. Wolff-Parkinson-White syndrome.
9. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements
10. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness must not be enrolled into this study.
11. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.
12. Any other conditions judged by the investigator that would limit the evaluation of a subject.

4.3 Subject Recruitment and Screening

Subjects will be identified through the clinical practices of the co-investigators or sub-investigators in the Division of Medical Oncology, Division of Radiation Oncology and Division of Otolaryngology at the Hospital of the University of Pennsylvania and its affiliated hospitals and through referrals from outside hospitals and physicians. The trial will be publicized on the

website of the Abramson Cancer Center of the Hospital of the University of Pennsylvania. This protocol will also be listed in ClinicalTrials.gov database. Subjects will be required to give written consent of study participation before any screening tests or evaluations are conducted.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects who do not complete the study protocol will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form (CRF). Final study evaluations will be completed at the time of discontinuation if it is possible. Reasons for withdrawal include, but are not limited to the following:

1. Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study;
2. Unacceptable toxicity: Subjects will be followed until resolution or stabilization;
3. Disease progression;
4. Subject withdraws consent;
5. Treatment delay greater than four weeks for any toxicity;
6. Subjects who do not have satisfactory compliance with study procedures;
7. Major protocol violations, including, but not limited to:
    a. failure to meet major inclusion/exclusion criteria;
    b. failure to complete full evaluations as required by protocol;
    c. use of concomitant therapies.

If any subject in a cohort discontinues early for reasons other than toxicity from immunotherapy, consideration will be given for replacement.

If a subject discontinues Study Treatments before completion of long term follow up for 6 months post the last dose of immunotherapy, all assessments for the end of Study Treatment visit and/or end of study visit should be performed.

Subjects who have disease progression confirmed and/or start new anti-cancer therapy will be discontinued from the study. In both Cohorts, subjects who progress in their disease, once confirmed, will be required to come for the end of the study visit. All subjects will be followed for survival status regardless of the cause of death.

In the case of a fatal outcome, all relevant information (including cause of death, autopsy report, ER/hospital record, concomitant medication, and relationship to Study Treatment or underlying disease) will be collected.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects taken off study due to treatment related toxicity will be followed until resolution or stabilization. All subjects will be followed for survival status regardless of the cause of death.

5 Study Drug

5.1 Description

Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study.

VGX-3100, the active investigational product to be used in this study, is a mixture of two separate DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18. INO-9012 is a DNA plasmid expressing the p35 and p40 human IL-12 subunits off of separate promoters within the same plasmid. VGX-3100 and INO-9012 combination is referenced as INO-3112.

INO-3112 (6 mg VGX-3100 + 1 mg INO-9012) is delivered by IM with EP for subjects in Cohort I and Cohort II. INO-3112 will be provided by Inovio Pharmaceuticals, Inc. or its designee.

Table 5.1 Investigational Products

Product	Concentration	Dosage Form & Route of Administration	Dose[a] (mL)
VGX-3100	6 mg/mL*	Sterile water for injection with 1% poly-L-glutamate sodium salt via IM injection	1.1[#]
INO-9012	10 mg/mL*	Sterile water for injection via IM injection	

*Target concentration of the DNA plasmid. The actual concentration may vary slightly in the lot used for this study.

[a]VGX-3100 and INO-9012 combined to deliver 1.1 mL (Cohorts I and II).

[#] There is no exception on dosing change in immunotherapy for any cohort

5.2 Packaging

VGX-3100 and INO-9012 vials will be shipped directly from the manufacturer or its designee to each individual study site or regional depot. Each vial will be labeled with a single panel label. Vials will only be handled by designated personnel (e.g. pharmacist) at each site. When a subject is eligible for enrollment, personnel will combine the appropriate investigational products as detailed in section 5.3.5 (Preparation of Investigational Product) then provide to the clinical personnel. Sample vial text for each investigational product is provided below:

VGX-3100	SynCon™ VGX-3100 [6mg/mL] 1 mL/vial Lot: VGX-3100. xxxxxx Date of Manufacture: DD MMM YY Final Retest Date: DD MMM YY Store frozen at or below -15C CAUTION: New Drug – Limited by Federal Law to Clinical Trial Use Only Inovio Pharmaceuticals Inc 660 W Germantown Pike, Plymouth Meeting, PA 19462 USA

INO-9012	SynCon™ INO-9012 [10 mg/mL] 0.2 mL/vial Single Use Vial Lot: INO-9012.xxxxxx Date of Manufacture: DD MMM YY Final Retest Date: DD MMM YY Store frozen at or below -15°C CAUTION: New Drug – Limited by Federal Law to Investigational Use. Inovio Pharmaceuticals Inc. Rev 000

5.3 Receiving, Storage, Dispensing and Return

5.3.1 Receipt of Drug Supplies

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the investigational product is adequate for the duration of the trial. Unless otherwise specified, the product will be shipped frozen on dry ice. If there is no dry ice remaining in the shipment container when the shipment is received Inovio, or its designee should be contacted immediately.

5.3.2 Storage

Investigational product(s) should be stored in a secure area according to local regulations. The product should be transferred from the shipping container to the appropriate storage conditions (frozen at -15ºC or below) upon arrival.

Freezer and refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

The principal investigator and study team will ensure that a current record of investigational product disposition is maintained at the study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

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

5.3.3 Dispensing of Study Drug

It is the responsibility of the Investigator to ensure that product is only dispensed to study participants. It must be dispensed only from official study sites by authorized personnel according to local regulations. The site will identify a dedicated investigational pharmacist to dispense IP. Their duties will include the receipt, storage, preparation and maintenance of records for the IP.

The VGX-3100 and INO-9012 vials should be removed from the freezer and thawed at room temperature to ensure complete thaw. The thawed product must be used within 4 hours of removal from freezer. All material removed from the freezer must not be re-frozen.

5.3.4 Precautions with Investigational Medicinal Product

A dose of the study product known or suspected to have been taken (accidentally or intentionally) exceeding the dose mandated by the protocol, and any misuse or abuse of study products or any other product taken as a concomitant medication, whether or not associated with an adverse experience, must be reported to Inovio Pharmaceuticals within 24 hours. Any clinical sequelae in association with the overdose should be reported as an AE or SAE. Details of signs or symptoms, clinical management, and outcome should be reported, if available.

5.3.5 Preparation of Investigational Product

Prior to administering to subjects the investigational products will be combined by authorized personnel into a single syringe using the following procedure:

Required Materials:
(1) or (2) vials SynCon™ VGX-3100, thawed
(1) vial SynCon™ INO-9012, thawed
(1) 2 mL sterile empty vial
(1) 0.5 mL or 1.0 mL syringes
(2) 3 mL syringes
(1) 21 gauge, 2” needle
(2) 21 gauge, 1.5” needles

Note: The second vial of SynCon™ VGX-3100 should only be thawed if less than 1.1 mL is withdrawn from the first vial in Step (1) below:

1. Using aseptic technique, withdraw the **entire contents** from the vial SynCon™ VGX-3100 with a 3 mL syringe and a 2” 21 gauge needle; a needle of a minimum length of 2” is recommended to be able to withdraw the entire contents of the larger vial.
2. If the volume of VGX-3100 in the syringe is **less than 1.1 mL**, perform Formulation Instruction Set A.
3. If the volume of VGX-3100 in the syringe is **exactly 1.1 mL**, perform Formulation Instruction Set B.
4. If the volume of VGX-3100 in the syringe is **1.2 mL or more**, perform Formulation Instruction Set C.

Formulation Instruction Set A (less than 1.1 mL VGX-3100 withdrawn):

1. Thaw a second vial of SynCon™ VGX-3100.
2. Once the vial is thawed, using the same syringe/needle from the first vial, withdraw a sufficient volume of VGX-3100 from the second vial to total **at least 1.2 mL** of VGX-3100 in the syringe.
3. Inject **1.2 mL** of VGX-3100 into an empty sterile vial; set this “mixing” vial which now contains 1.2 mL of VGX-3100 aside.

4. Using a new 0.5 or 1.0 mL syringe with a 1.5" 21 gauge needle, withdraw **0.12 mL** from the vial SynCon™ INO-9012 and add the 0.12 mL to the "mixing" vial containing 1.2 mL of VGX-3100. The final volume of this vial should now be approximately 1.32 mL of VGX-3100 and INO-9012.
5. Ensure the contents of the "mixing" vial are well mixed by gently inverting the vial several times.
6. Using a 3 mL syringe with a 1.5" 21 gauge needle, withdraw **1.1 mL** of VGX-3100 and INO-9012 from the "mixing" vial. This syringe will be used for dosing of subjects.

Formulation Instruction Set B (exactly 1.1 mL VGX-3100 withdrawn):

1. Inject **1.1 mL** of VGX-3100 into an empty sterile vial; set this "mixing" vial which now contains 1.1 mL of VGX-3100 aside.
2. Using a new 0.5 or 1.0 mL syringe with a 1.5" needle, withdraw **0.11 mL** from the vial SynCon™ INO-9012 and add the 0.11 mL to the "mixing" vial containing 1.1 mL of VGX-3100. The final volume of this vial should now be approximately 1.21 mL of VGX-3100 and INO-9012.
3. Ensure the contents of the "mixing" vial are well mixed by gently inverting the vial several times.
4. Using a 3 mL syringe with a 1.5" 21 gauge needle, withdraw **1.1 mL** of VGX-3100 and INO-9012 from the "mixing" vial. This syringe will be used for dosing of subjects.

Formulation Instruction Set C (1.2 mL or more of VGX-3100 withdrawn):

1. Inject **1.2 mL** of VGX-3100 into an empty sterile vial; set this "mixing" vial which now contains 1.2 mL of VGX-3100 aside.
2. Using a new 0.5 or 1.0 mL syringe with a 1.5" needle, withdraw **0.12 mL** from the vial SynCon™ INO-9012 and add the 0.12 mL to the "mixing" vial containing 1.2 mL of VGX-3100. The final volume of this vial should now be approximately 1.32 mL of VGX-3100 and INO-9012.
3. Ensure the contents of the "mixing" vial are well mixed by gently inverting the vial several times.
4. Using a 3 mL syringe with a 1.5" 21 gauge needle, withdraw **1.1 mL** of VGX-3100 and INO-9012 from the "mixing" vial. This syringe will be used for dosing of subjects.

Replace the 1.5" needle with 2" 21 gauge needle of the syringe for dosing of subjects. The syringe must be labeled with a four-hour expiration time from the time the vial is removed from the freezer. The label should also contain the words "administer as soon as possible".

5.3.6 Return or Destruction of Study Drug

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to Inovio Pharmaceuticals, Inc., or its designee, if not authorized by Inovio Pharmaceuticals, Inc. to be destroyed at the site. All investigational products returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc. It is the Investigator's responsibility to arrange for

disposal for all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

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

5.4 Use of CELLECTRA® Electroporation Device

The instructions for use of the CELLECTRA® device are located in the Operations Manual. Each clinical site will receive training for the use of the CELLECTRA® device. The following specifications will be used during the study:

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Maximum Voltage Strength = 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second
EP needle array length (injection depth) ~12 mm (with array guide in place)
~18 mm (without array guide)

5.4.1 Investigational Device Accountability

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the CELLECTRA®5P serial number, applicator serial number, and array lot number used for electroporation of each subject.

6 Study Procedures and Treatments

6.1 Cohort I

Immunotherapy will be performed prior to and after definitive surgery. Up to 2 doses may be administered approximately once every 3 weeks (+/-3 days), depending on the planned interval between pre-surgery evaluation and definitive surgery according to standard practice. Up to 3 doses will be given post-surgery. All subjects will receive a total of 4 doses of immunotherapy.

6.1.1 Pre treatment evaluation (Screening; Done Within 28 days of First Dose)

1. Signed written informed consent.
2. Complete medical history including prior and current medications/treatments.
3. Complete physical examination including, but not limited to vital signs, height, weight and oxygen saturation.
4. ECOG Performance Status.

5. Tumor Evaluation: Confirmation of diagnosis by histology and confirmation of p16 positivity. While biopsy tissue samples are undergoing confirmation of p16 positivity, the subject may proceed to other screening procedures and tests. However, the subject will be dosed only upon confirmation of p16 positivity or other pathological evidence of oncogenic HPV infection. Confirmation of diagnosis of surgically resectable HNSCCa.
6. 12-lead ECG.
7. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, PT, INR/PTT, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin and CPK.

   Note: If clinical lab testing is performed within 28 days prior to study Day 0 as standard of care, the results can be used for screening and eligibility assessment.

8. Serology (HIV Ab, HCV Ab, HBsAg).
9. Serum beta HCG (for women of child bearing potential).
10. Adverse Events
11. Whole blood and serum for baseline immunologic assays.
12. Paraffin-embedded tumor tissue or unstained slides for ISH and IHC.

On the rare occasions where a subject is re-screened, the clinical labs and 12-lead ECG must be repeated unless they occur within 4 weeks of the subject's first dose. All other screening procedures do not need to be repeated.

6.1.2 Visit for Immunotherapy (Pre and Post surgery: Every 3 weeks ± 3 days)

Subjects may receive up to 2 doses of immunotherapy prior to surgery and 1-3 doses post-surgery as previously described. All sequential doses will be administered three weeks (±3 days) apart.

The following study evaluations will be performed **prior to immunotherapy**:

1. Confirmation of p16 positivity or other pathological evidence of oncogenic HPV infection.
2. Medical/Clinical assessment including concomitant medications/treatments.
3. Focused physical examination including, but not limited to vital signs, weight and oxygen saturation.
4. ECOG Performance Status.
5. Review of adverse events.
6. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium and serum albumin.

   NOTE: If clinical screening labs (CBC and Chemistry) were performed within 72 hours prior to the subject's first immunotherapy, these labs are not required to be redrawn prior to the subject's first immunotherapy.

7. Urine β-HCG (for women of child bearing potential) up to 72 hours prior to visit.
8. Whole blood and serum for baseline immunologic assays.

The following study evaluations will be performed on the same day **post-immunotherapy**:

1. Injection site reaction assessment within 30-45 minutes after EP.
2. Review of adverse events.
3. Data should be downloaded from the EP device.
4. Distribute participant reminder card to be reviewed at the next visit.

6.1.3 Surgery

At the time of definitive surgery, fresh resected tumor specimens not needed for diagnostic purposes and unstained slides will be collected and will be used for correlative studies and evaluation of immune responses. Prior to surgery whole blood and serum will also be collected for immunologic assays.

6.1.4 Post surgery 2 week follow up (± 7 days)

1. Medical/Clinical assessment including concomitant medications/treatments.
2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Whole blood and serum for immunologic assays.

6.1.5 Inspection Visit 4 Weeks Post-Surgery (±7 days)

1. Medical/Clinical assessment including concomitant medications/treatments
2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Visual Inspection of wound healing.
6. Whole blood and serum for immunologic assays.

6.1.6 2 Week Follow Up Post Last Dose of Immunotherapy (±3 Days)

1. Medical/Clinical assessment including concomitant medications/treatments
2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status
4. Review of adverse events.
5. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin and CPK.
6. Injection site reaction assessment.
7. Whole blood and serum for immunologic assays.

6.1.7 Long term follow up (every 3 months ±7 days for 6 months)/End of study visit

Long term follow up for 6 months from the last dose of immunotherapy. End of study visit will be the last long term follow up visit.

1. Medical/Clinical assessment including concomitant medications/treatments.
2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium and serum albumin.
6. Whole blood and serum for immunologic assays.

6.2 Cohort II

Immunotherapy will start approximately 2-6 months after completion of chemoradiation therapy.

6.2.1 Pre-treatment evaluation (Screening; within 28 days of first dose)

1. Signed written informed consent.
2. Complete medical history including prior and concurrent medications/treatments.
3. Complete physical examination including, but not limited to vital signs, height, weight and oxygen saturation.
4. ECOG Performance Status.
5. Tumor Evaluation: Confirmation of diagnosis by histology and confirmation of p16 and HPV -16 and/or -18 (by PCR or ISH assay) positivity.
6. 12-lead ECG (performed up to 4 weeks prior to Dose 1).
7. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, PT, INR/PTT, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium and serum albumin and CPK

   Note: If these testing are performed within 28 days prior to study Day 0 as standard of care, the results can be used for screening and eligibility assessment.

8. Serology (HIV Ab, HCV Ab, HBsAg).
9. Serum beta HCG (for women of child bearing potential)
10. Whole blood and serum for baseline immunologic assays.
11. Paraffin-embedded tumor tissue or unstained slides for IHC.

If clinical screening labs (CBC and Chemistry) were performed within 72 hours prior to the subject's first immunotherapy, these labs are not required to be redrawn prior to the subject's first immunotherapy.

6.2.2 Visit for Immunotherapy (4 doses Every 3 Weeks ±3 days)

The following study evaluations will be performed **prior to immunotherapy:**

1. Medical/Clinical assessment including concurrent medications/treatments.
2. Focused physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Clinical laboratory testing including but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium and serum albumin. Urine β-HCG (for women of child bearing potential).

   NOTE: If clinical screening labs (CBC and Chemistry) were performed within 72 hours prior to the subject's first immunotherapy, these labs are not required to be redrawn prior to the subject's first immunotherapy.

6. Whole blood and serum for baseline immunologic assays.

The following study evaluations will be performed on the same day **post-immunotherapy:**

1. Injection site reaction assessment within 30-45 minutes after EP.
2. Review of adverse events.
3. Data should be downloaded from the EP device
4. Distribute participant reminder card to be reviewed at the next visit.

6.2.3 2 Week Follow Up Post Last Dose of Immunotherapy (± 3 days)

1. Medical/Clinical assessment including concurrent medications/treatments.
2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Injection site reaction assessment.
6. Clinical laboratory testing including but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin and CPK.
7. Whole blood and serum for immunologic assays.

6.2.4 Long Term Follow Up (Every 3 Months ± 7 Days for 6 months)/End of study visit

Long term follow up for 6 monthss post the last dose of immunotherapy. End of study visit will be the last long term follow up visit

1. Medical/Clinical assessment including concurrent medications/treatments.

2. Complete physical examination including, but not limited to vital signs, weight and oxygen saturation.
3. ECOG Performance Status.
4. Review of adverse events.
5. Clinical laboratory testing including, but not limited to: CBC with differential and platelet count, total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium and serum albumin.
6. Whole blood and serum for immunologic assays.

6.3 Timing and Evaluation

6.3.1 Informed Consent

Study personnel will meet with prospective study subjects, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, and study treatments and follow-up procedures. The subjects must sign the ICF before the study can commence.

6.3.2 Assignment of Subject Numbers

Study personnel will screen subjects and assign allocation numbers as appropriate. Each subject who consents will be assigned a patient identification number (PIN) which identifies the subject for all study-related procedures for the duration of their participation in the study. Once assigned, PINs cannot be reused for any reason

6.3.3 Medical History/Existing Events/Illnesses

Investigators should document all relevant and clinically significant non-cancer related illnesses that the subject has experienced within 5 years prior to screening and all prior cancer related illnesses as Medical History. The determination of the relevance includes, but not limited to, the history related to HNSCCa and treatment for HNSCCa, major surgery and procedures, on-going medical conditions that require continuous treatment or close follow up/monitoring, history of hypersensitivity and allergic events.

Illnesses' first occurring or detected after the ICF is signed or during the study and/or worsening of an existing illness during the study are to be documented as AEs on the CRF.

Prior treatments, defined as administered prior to first immunotherapy treatment, should be recorded in the CRF as prior medications. Concomitant treatments, defined as treatments continued by the subject upon entry into the study and new treatments taken after the first immunotherapy treatment, should be recorded in the CRF as concomitant medications.

The subject's previous anti-cancer treatments, including detailed information about their therapy directed against HNSCCa (e.g. past surgical and/or radiation regimens) should be documented. Additionally, information about any non-cancer treatments should also be noted.

6.3.4 Safety Assessments

The following subject evaluations for safety will be performed.

6.3.4.1 Participant Reminder Card

Subjects record any post treatment reactions and enter this information on the participant reminder card. The study staff will review the reminder card and assess the reported events for clinical significance.

Study staff should evaluate each unique reminder card entry according to CTCAE guidelines (Version 4.03) and Table 6.1 of the protocol, "Grading Scale for Injection Site Reactions." Any reminder card entry determined to meet the criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. If the reminder card entry does not meet the criteria of a Grade 1 or higher AE as per the CTCAE guidelines, clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the reminder card entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.3.4.2 Medical/Clinical Assessments and concomitant medications

New onset disease and concomitant medications will be queried from the first time reported through to the end of study visit/discharge.

Assessment of adverse events will be collected from the time of informed consent through End of Study visit and will be assessed using the "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010.

6.3.4.3 Physical Assessments

A complete physical examination will be conducted at specified visits. A targeted physical assessment will be performed at other visit as determined by the Investigator or directed per subject complaints. The injection site is to be assessed by the study personnel within 30 – 45 minutes after EP, and during subsequent clinic visits as specified in the schedule of events (Tables S1 and S2).

6.3.4.4 Vital Signs

Vital signs may include but are not limited to, body temperature, oxygen saturation, blood pressure and heart rate will be measured at specified visits.

6.3.4.5 Weight and Height

Weight (kg) and height (cm) will be collected at specified visits. The information can be used for body mass index (BMI) calculations.

6.3.4.6 12-Lead ECGs

An ECG will be performed within 28 days of the first dose of immunotherapy for eligibility.

6.3.4.7 Pregnancy Test

Women of reproductive potential must have a negative serum β-HCG test at screening and a negative serum or urine (with sensitivity of at least 25 mIU/mL) β-HCG within 72 hours prior to administration of immunotherapy. If at any point the β-HCG test is positive, indicating that the subject is pregnant, no additional immunotherapy will be administered, but the subject will be followed for the duration of the study and beyond to determine the outcome of the pregnancy (with the subject's consent).

6.3.4.8 Eastern Cooperative Oncology Group (ECOG)

ECOG performance status will be measured at specified visits.

6.3.4.9 Laboratory Evaluations

Blood samples will be taken to be tested for serum chemistry and complete blood count as specified in the Schedule of Events (Tables S1 and S2).

Complete Blood Count
White blood cell (WBC) count with differential, Red blood cell (RBC) count, Hemoglobin, Hematocrit, Platelet count and PT, INR/PTT (screening only).

Serum Chemistry
Bilirubin, alkaline phosphatase, SGPT (serum glutamic-pyruvic transaminase)/ALT, SGOT (serum glutamic-oxaloacetic transaminase)/AST, creatinine, electrolytes, calcium, albumin and CPK (at screening and at 2 weeks after the last dose of immunotherapy only).

Serology (screening only):
Antibody to human immunodeficiency virus (HIV-Ab), hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (HCV)

6.4 Optional collection of Leftover Tumor Tissue Sample

Leftover tumor tissue samples may be collected through subject's standard of care during the course of the study. The tumor tissue samples will be used for immunological and correlative assessments.

6.5 HLA Testing

HLA testing will be performed on PBMC from any single blood sample collected for immunogenicity analysis after screening visit. If the subject has a record of previous high resolution HLA testing and access to results, this HLA testing is not required.

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

6.6 Injection of INO-3112 Followed by Electroporation

INO-3112 will be administered, mixed in a volume of 1.1 mL by IM injection in the deltoid followed immediately by EP. If the deltoid is not a suitable location, the IM injection should be in the lateral quadriceps followed immediately by EP. Vaccination/EP must not be given within 2 cm of a tattoo, scar, or active lesion/rash or on the same side of the body where an implanted device is located. The timing of the initial dose will be as outlined above.

The vaccination/electroporation procedure will be performed by qualified personnel. An individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to subjects (licensed health care professionals who have appropriate credentials, e.g. MD, DO, RN, NP, PA) in addition to satisfactorily completing device training from device company personnel. Individuals whose credentials do not meet the relevant local requirements may perform the /electroporation procedure under one or both of the conditions below:

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

Any deviation from the above procedures must be approved by the Inovio Pharmaceuticals, Inc. or its designee.

6.6.1 Management of anxiety and pain due to EP procedure

Subjects will be offered topical anesthetic (e.g. EMLA), to limit significant discomfort from the vaccination/EP procedure. If EMLA (lidocaine 2.5% and prilocaine 2.5%) is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to vaccination/EP. Subjects will be offered an analgesic (e.g. ibuprofen, ketorolac) after vaccination/EP. In case subjects are anxious for the procedure, they will be offered a mild sedative (e.g. 0.5-1.0 mg lorazepam), or equivalent, as a mild sedative for anxiety related to the vaccination/EP procedure. Mild sedatives may be administered approximately 1 hour prior to EP. Subjects who receive a mild sedative should not operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site. Subjects who are allergic to or have contraindications to EMLA, ibuprofen, ketorolac or a mild sedative will be offered a suitable alternative.

6.6.2 Assessment of Injection Site Reactions

When evaluating injection site reactions throughout the study, the investigator or designee will be instructed to use the following grading scale (Table 6.1):

Table 6.1: Grading Scale for Injection Site Reactions

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

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

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

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

7 Statistical Plan

7.1 Sample Size Determination

A minimal of 20 but no more than 25 eligible subjects will be enrolled, as described above. This study is an estimation study, and as such, a power calculation is not applicable. Regarding the primary analysis, 20 subjects will provide 95% confidence that the true incidence of SAEs is <17% if 0 SAEs are observed. If more than one subject in a cohort discontinues early for reasons other than toxicity from the immunotherapy, consideration will be given for replacement.

7.2 Statistical Methods

The primary analysis will estimate safety parameters. The incidence of SAEs and the incidence of injection site reactions will be estimated along with exact Clopper Pearson 95% confidence intervals. Toxicity experience will also be recorded and summarized.

In secondary analyses, immune response parameters will be estimated. For continuous outcomes, the mean and 95% confidence interval will be calculated using a t-distribution approach, and for binary outcomes, the proportion and exact Clopper Pearson 95% confidence interval will be calculated.

In exploratory analyses, we will also estimate the distributions of progression-free survival (PFS) and overall survival (OS) will be estimated, and any observed anti-tumor responses will be summarized. PFS and OS will be measured from the time of instillation of the initial dose of immunotherapy. Both The variables will be potentially censored by the end of the subject's observation. These distributions will be summarized using Kaplan-Meier survival curves and estimated median time to event of each type. Anti-tumor response category frequencies will be calculated.

7.3 Subject Population(s) for Analysis

Any subject who receives at least one dose of treatment will be included in the safety analyses. For immunogenicity and survival/anti-tumor analyses, the main analyses will utilize subjects who received their assigned number of doses.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.1.2 Adverse Event

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting Study Treatment. An unexpected AE is one not identified in the Clinical Investigator's Brochure (CIB) or otherwise not expected from the characteristics of the clinical material.

AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after the first screening visit (before the administration of study drug)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy;
- All AEs that occur from the screening visit onwards and throughout the duration of the study, including the follow-up off study treatment period should be recorded as an AE

AEs do not include the following:

- Medical or surgical procedures other than the definitive surgical procedure for Cohort I (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visits that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF
- Uncomplicated pregnancy (documented on a pregnancy CRF)
- An induced elective abortion to terminate a pregnancy without medical reason (documented on a pregnancy CRF)

8.1.3 Serious Adverse Event

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

- Death during the period of surveillance defined by the protocol;

- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE (see Section 8.1.12);
- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; development of malignancies.

Clarification of Serious Adverse Events

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

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

Serious adverse events that are ongoing should be followed until resolution. The reporting period for SAEs is described in Section 8.3.

8.1.4 Adverse Event Reporting Period

0-3 days after each Study Treatment. Study subjects will be directly observed by study personnel for 30-45 minutes after administration of Study Treatment for immediate reactions. The occurrence and severity of any AE during this period or the lack of same will be recorded. After

that, subjects will be given an oral thermometer and a Participant Reminder Diary. They will be asked to take and record their body temperature daily at the same time and to note and characterize in their own words any local or systemic events they experience, during this 3 day period after each Study Treatment.

Throughout the Study. In addition to the daily record of oral temperature, administration site reactions, and systemic complaints recorded for 3 days after Study Treatment or until resolution, subjects will be queried at each study visit regarding the occurrence of any SAE or other AE that may have occurred since the last study visit. They will be reminded to contact study personnel and immediately report any such event that occurs during the course of the study. These events will be recorded on the CRFs.

The investigator will grade laboratory AEs and clinical AEs (based on discussions with study participants) with respect to the following levels of severity as defined in the document "Common Terminology Criteria for Adverse Events (CTCAE)", NCI version 4.03 issued by the US Department of Health and Human Services:

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

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

8.1.5 Causal Relationship of Clinical Material to Adverse Events

A related AE is one judged to have a suspected relationship to the administration of the clinical material, (INO-3112) and the investigational CELLECTRA® device. An AE may also be assessed as not related to the investigational product. The Investigator is responsible for reporting adverse events and causality (judging the relationship between the administration of the clinical material and a subsequent AE) because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the investigational product, and monitors the subject's response to the investigational product. The Investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the investigational product and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the Study Subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. Causality should be assessed by the Investigator as "yes, related" or "no, unrelated" by the following criteria:

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

The following guidance should also be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug;
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event;
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For Study Subject receiving combination therapy, causality may be assessed individually for each protocol-mandated therapy or for the combination.

8.1.6 Preexisting Condition

A preexisting condition is one that is present at the time of signing of Informed consent. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1.7 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.1.8 Post-study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol-required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion of termination visit and the event is deemed by the investigator to be related to the study treatment (following the guidelines in Section 8.1.5), he/she should promptly document and report the event to Inovio Pharmaceuticals.

8.1.9 Abnormal Laboratory Values

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, coagulation, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 8.1.2 and 8.1.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- Requires therapeutic intervention or diagnostic tests

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

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

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

8.1.10 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event as detailed in 8.1.3. Any condition related to surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. Adverse events will be measured and graded in accordance with the document entitled "Common Terminology Criteria for Adverse Events (CTCAE)", NCI version 4.03 issued by the US Department of Health and Human Services on June 14, 2010.

All AEs, regardless of severity, seriousness, or presumed relationship to study treatment, must be recorded using medical terminology in source documents and on the CRF. Whenever possible, a diagnosis should be documented, in lieu of symptoms. The source document and the CRF must contain the investigator's opinion concerning the relationship of the AE to study treatment.

AEs should be described with the following attributes:

- Duration (start and end dates)
- Seriousness
- Severity
- Causality
- Action(s) taken
- Outcome

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must confirm to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to investigational product(s),
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the grade and association between the event and study treatment

8.3.1 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) will be defined as treatment- or EP-related adverse events including any of the following:

1. Grade 3 or greater injection site pain, tenderness, erythema, and/or induration recorded ≥ 1 hour after study treatment (see Table 6.1)
2. Grade 3 or greater fever within 7 days of study treatment
3. Grade 3 or greater systemic symptoms within 7 days of study treatment

as defined in the "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010. The worst grade for that particular event is to be documented on the CRFs.

Sites should inform Inovio of any ERER within 72 hours to discuss whether further dosing should continue for that participant.

8.3.2 Stopping Rules (Criteria for Pausing of Study)

8.3.2.1 If at any time during the study one third (1/3) or more subjects experience an ERER assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be on hold immediately until a thorough investigation has been conducted by the Medical Monitors of Inovio and Principal Investigator.

8.3.2.2 Any SAE, potentially life threatening AE or death assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be on hold immediately until a thorough investigation has been conducted by the Medical Monitors of Inovio and Principal Investigator and IRB (if applicable).

8.3.2.3 If three or more subjects in this study, experience the same grade 3 or 4 adverse event, assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be on hold immediately until a thorough investigation has been conducted by the Medical Monitors of Inovio and Principal Investigator.

8.3.2.4 In the event of any unexpected Grade 4 toxicities, assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be on hold immediately until a thorough investigation has been conducted by the Medical Monitors of Inovio and Principal Investigator and IRB (if applicable).

8.3.2.5 The study will be on hold for any report of Grade 3 anaphylaxis from immunotherapy/EP in two or more subjects (as graded per "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010). Occurrence in three or more subjects will lead to an immediate halt of enrollment and further immunotherapy until full discussion has been conducted by the Medical Monitors of Inovio and Principal Investigator, IRB (if applicable) and the FDA.

8.3.3 Investigator reporting: Inovio Pharmaceuticals, Inc.

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to Inovio within 24 hours of the event. To report such events, the SAE worksheets or a MedWatch 3500a form must be completed by the investigator and faxed/emailed to Inovio within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by facsimile/email to:

TELEPHONE:	[redacted]
EMAIL:	safety@inovio.com

If there is a need to directly contact the medical monitor, please contact:

MEDICAL MONITOR:	[redacted], MD or designee	MAILING ADDRESS:
TELEPHONE:	[redacted] office	Inovio Pharmaceuticals, Inc.
	[redacted] Mobile	660 W. Germantown Pike,
FACSIMILE (FAX):	[redacted]	Suite 110
EMAIL:	[redacted]	Plymouth Meeting, PA 19462

As soon as available, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include an updated MedWatch Form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to Inovio.

Inovio will be responsible for reporting any applicable events to the U.S. Food and Drug Administration (FDA) per their reporting requirements.

8.3.4 Investigator Reporting: the Penn IRB

The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Deaths occurring for subjects on-study and within 30 days of study drug administration that are considered unforeseen and indicates participants or others are at increased risk of harm (i.e. unexpected and probably/definitely related), must be reported to the IRB within 24 hours of notification. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.3.5 Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

[redacted], Institutional Review Board
[redacted]
Phone: [redacted]
Fax: [redacted]

8.4 Reportable Events

Deviation

A one-time **unintentional** action or process that departs from the IRB approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the

safety and welfare or the subjects, the deviation must be reported to the Sponsor (Inovio) as soon as possible.

8.5 Reporting of Device Related Complaints

Any problems experienced during the treatment procedure including potential malfunctions of the CELLECTRA® device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure should be reported to the Sponsor or designee immediately for evaluation via email to [redacted]. The Error Reporting Form provided will be completed and sent to Inovio or its designee.

9 Data Handling and Record Keeping

9.1 Confidentiality

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

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

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

9.2 Source Documents

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

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or

contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the drug manufacturer. In such an instance, it is the responsibility of the drug manufacturer to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring

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

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure compliance with all applicable requirements
- All clinical site monitoring visits will be documented
- Periodic site visits will be performed throughout the study
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
    - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/EC policies
    - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB/EC
    - Inspect all Case Report Form (CRF) pages for completeness, logic, and internal consistency throughout the study
    - Assure that the study facilities continue to be acceptable
    - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that test article accountability and reconciliation records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing

10.2 Medical Monitor

The medical monitor for this study will be Dr. [redacted] from Inovio Pharmaceuticals or a designee.

10.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the IND Sponsor or its designee, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Inovio Pharmaceuticals before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

The study will be supported by funds through the Abramson Cancer Center's **EARLY PHASE CLINICAL RESEARCH SUPPORT**. Funding for immunological correlatives and vaccine will be provided by Inovio Pharmaceuticals, Inc. We will not be receiving additional funding through Inovio.

12.2 Conflict of Interest

Investigators on this protocol do not have a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) All University of Pennsylvania investigators will follow the University conflict of interest policy.

13 Publication Plan

Publication policy shall be as provided in Section 4.3 of the Clinical Trial Agreement between the University of Pennsylvania and Inovio Pharmaceuticals, Inc.

14 List of Abbreviations

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
CBC	Complete Blood Count
Chemo XRT	Chemoradiation Therapy
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell Mediated Immunity
CPK	Creatine Phosphokinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
EP	Electroporation
FDA	Food and Drug Administration
HBsAg	Hepatitis B Surface Antigen
HNSCCa	Head and Neck Squamous Cell Carcinoma
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISH	In Situ Hybridization
IUD	Intrauterine Device
IM	Intramuscular
IP	Investigational Product
LFT	Liver Function Test
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction

RBC	Red Blood Cells
SAE	Serious Adverse Event
SFU	Spot Forming Units
SOC	System Organ Class
TILs	Tumor Infiltrating Lymphocytes
ULN	Upper Limit of Normal
WBC	White Blood Cells

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