ClinicalTrials.gov ID NCT04398433

Sponsor Inovio Pharmaceuticals

TITLE: INO-3107 With Electroporation (EP) in Participants With HPV-6- and/or HPV-11-Associated Recurrent Respiratory Papillomatosis (RRP)

DATE: 22 August 2024

RRP-001

An open-label multi-center study of INO-3107 with electroporation (EP) in subjects with HPV-6- and/or HPV-11-associated recurrent respiratory papillomatosis (RRP)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND#: 19508

Protocol Version: 4.0

Protocol Version Date: 23 July 2021

Medical Monitor Approval Page

Drug: INO-3107

Sponsor: Inovio Pharmaceuticals, Inc.
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Medical Monitor: Jeffrey Skolnik, MD
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Inovio Pharmaceuticals, Inc.

Approval Signature:

Jeffrey Skolnik, MD
Senior Vice President, Clinical Development
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

Principal Investigator Acknowledgement

I have read and understood this Protocol and agree that it contains all details necessary to conduct the clinical trial. I understand that it must be reviewed by the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial and approved or given favorable opinion before implementation.

The Principal Investigator's (PI's) signature constitutes the PI's approval of this Protocol and provides the necessary assurances that this clinical trial will be conducted in accordance with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), local legal and regulatory requirements, and all stipulations of the Protocol.

Principal Investigator Signature:

Principal Investigator Printed Name

Principal Investigator Signature

Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

SUMMARY OF CHANGES

The following are a list of protocol changes from Version 3.0 dated 12 April 2021 to Version 4.0 dated 23 July 2021. Changes not listed in this summary are administrative and do not affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. This protocol amendment adds an additional 10 subjects to the study to explore the use of the Side Port Needle. The Side Port Needle is described in Section 1.2 of the protocol and has been referenced in Sections 5.1.3, 5.3.2, 5.5, and 6.5 .
2. Section 6.4.4 has been updated to add serum bilirubin to the list of serum chemistry analytes at Day 0, Weeks 3, 6, and 9. This was inadvertently not included.
3. Formatting and grammar have been edited throughout.

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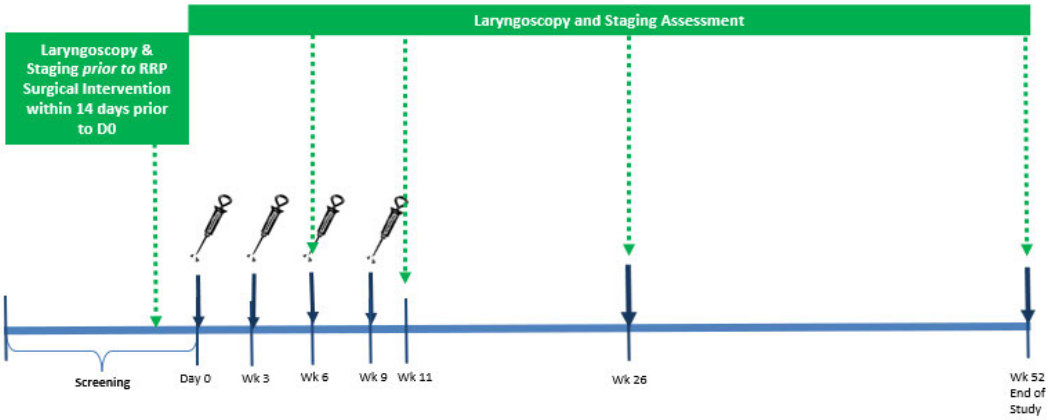
CLINICAL PROTOCOL SYNOPSIS

Protocol Title: An open-label multi-center study of INO-3107 with electroporation (EP) in subjects with HPV-6- and/or HPV-11-associated recurrent respiratory papillomatosis (RRP)
Protocol Number: RRP-001
Clinical Trial Phase: 1/2
Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 12 sites in the US
Clinical Trial Design: This is a Phase 1/2 open-label, multicenter trial to evaluate the safety, tolerability, immunogenicity, and efficacy of INO-3107 in subjects with HPV-6 and/or HPV-11-associated RRP. INO-3107 will be administered IM followed by EP in subjects at Day 0, Weeks 3, 6, and 9. Approximately 20 subjects will receive INO-3107 via standard needle, followed by approximately 10 subjects who will receive INO-3107 via the Side Port Needle.      This study will enroll approximately 30 adults (≥18 years old) who have been diagnosed with either Juvenile-Onset RRP (J-O RRP) as defined by age at first diagnosis <12 years or with Adult-Onset RRP (A-O RRP) as defined by age at first diagnosis ≥12 years. This study will have a safety-run in: Up to six subjects will be enrolled with a one week waiting period between each enrolled subject. Each subject will be assessed up to Week 6. Once the first three subjects of up to these six have completed Week 6 assessments, in the absence of dose-limiting toxicity (DLT), subject enrollment may begin in full after review of safety data and discussion between the Sponsor's Medical Monitor and the Investigator(s) at the subjects' site. However, if prior to the first three to six subjects completing Week 6, a single subject from the first six experiences a DLT then enrollment will be limited to six subjects until all six subjects have reached Week 6 and are assessed for DLT. If a second subject within the first 6 experiences a DLT within the first 6 weeks, enrollment will stop, and the Sponsor's Medical Monitor and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to cease further enrollment. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the respective study IRBs. Enrollment will continue until approximately 30 subjects are enrolled.

Safety and tolerability will continue to be assessed throughout the study after initial tolerability has been established in the first six subjects. If more than two subjects experience a DLT at any time during the study, after the initial six subjects are enrolled, the Sponsor will pause enrollment until further discussion with the site Investigator determines that the study may reopen to enrollment.

Tolerability will be determined by the reported incidence of dose-limiting toxicity (DLT), which is defined as:

- Treatment-related NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade ≥3 non-hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours, or;
- Treatment-related NCI CTCAE v5.0 Grade ≥3 hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours.

Additionally, enrollment and additional dosing will be paused until Sponsor discussion with the site Investigator determines that enrollment and dosing may continue if the following CTCAE v5.0 events are reported at any time in the study:

- One Grade 4 or 5 related SAE;
- Two Grade 3 related SAEs

Subjects will undergo routine surgical procedure for removal of papilloma(s) during the screening period within 14 days prior to Day 0 dosing (papilloma removal and Day 0 dose may be performed same day if other eligibility criteria have been fulfilled). Biopsy tissue will be collected and sent to [redacted] for evaluation of secondary and exploratory endpoints. Archival tissue (slides or blocks) obtained within one year of the screening window may be used, or a biopsy conducted during routine surgery.

Status of disease during the trial will be monitored by the Investigator during laryngoscopy, including documentation with Staging Assessment scores. If at any time during the trial, surgical removal (including laser) of papilloma is clinically indicated per PI judgement, the subject may undergo procedure for papilloma removal, but this must be captured on the electronic case report form.

Documentation of the Staging Assessment score prior to surgery is required, and explanation for requirement of surgical removal of papilloma must be documented. Surgical interventions during the trial must be documented to include information about the appearance and location of tissue being removed and instruments used. Video/photographic documentation of laryngoscopy is required.

This trial will not utilize a Data Safety Monitoring Board. This is a single-arm, open-label trial. The Sponsor will have access to unblinded safety and tolerability data during the trial. At a minimum, the Sponsor's Medical Monitor will review reported adverse events quarterly.

Criteria for Evaluation:

Research Hypothesis: INO-3107, [redacted] delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 will be generally safe and well-tolerated in subjects with recurrent respiratory papillomatosis secondary to HPV-6 and/or HPV-11.

Primary Objective: To evaluate the safety and tolerability of INO-3107 in subjects with HPV-6 and/or HPV-11- associated RRP.

Primary Endpoint: Safety and tolerability as assessed by reported adverse events (AE) and serious adverse events (SAE).

Secondary Objective(s):

1. To evaluate the efficacy of INO-3107, as determined by the frequency of RRP surgical interventions in the year following the first dose of investigational product, compared to the frequency in the year prior to Day 0.
2. To evaluate the efficacy of INO-3107 as assessed by changes in the RRP Staging Assessment over time.
3. To evaluate the cellular immune response to INO-3107 when given IM, followed by EP.
4. To evaluate the immunogenicity of INO-3107 as assessed by pro-inflammatory and immunosuppressive elements in resected tumor tissue at study entry and, if available, at subsequent tissue resections.
5. [redacted]

Secondary Endpoint(s):

1. Number of RRP surgical interventions in the one year following Day 0, compared to the one year prior to Day 0.
2. Changes in Staging Assessment as measured by the RRP Staging Assessment score over time.
3. Antigen-specific cellular immune responses assessed by:
    - IFN-γ secreting cells in peripheral blood mononuclear cells (PBMCs) by ELISpot
    - T cell phenotype and lytic potential in PBMCs by flow cytometry
4. Assessment of pro-inflammatory and immunosuppressive elements in resected tumor tissue, if available.
5. [redacted]

[redacted]

[redacted]

Safety Assessment: Subjects will be followed for safety from the time of signing informed consent through Week 52, or the subject's last visit. All adverse events including SAEs, UADEs, DLTs and other AEs will be recorded. Clinically significant changes in laboratory parameters and vital signs from baseline assessments will be assessed.

Efficacy Assessment: A detailed medical history will be obtained for each subject which will include documentation of HPV-6 and/or HPV-11 RRP, a list of RRP surgeries and therapies occurring within 3 years prior to screening, and any periods of remission. Subjects must have had at least two surgical RRP interventions (including laser) in the year prior to and including Day 0, to be eligible for the trial. Subjects must require RRP intervention at the time of entry into this study and will undergo routine surgical removal of their papilloma(s) during screening, within 14 days prior to Day 0 dosing, to maximize standardization of baseline staging across subjects.

The efficacy assessment will be based upon the number of RRP surgical interventions in the 52 weeks post Day 0 compared to the number of RRP surgical interventions in the year prior to Day 0 dosing. RRP surgical interventions include laser therapies. The trial will also evaluate changes in RRP Staging Assessment over time.

Immunogenicity Assessment: The trial will explore humoral and cell mediated immune responses in blood samples taken at baseline (i.e. Screening and Day 0 prior to dosing) and Weeks 6, 9, 11, 26, and 52. Tissue samples will be collected at baseline and if clinically indicated during the study. [redacted]

Virologic Assessment: The trial will evaluate the presence of HPV-6/11 DNA in tissue samples and peripheral blood, prior to and following study treatment, as described.

Clinical Trial Population: Subjects with HPV-6- and/or HPV-11-associated RRP, who require at least two surgical interventions per year for the past year (minimum), for removal of associated papilloma(s). Approximately 30 adult subjects (aged 18 and older) diagnosed with Juvenile-Onset RRP (age at diagnosis <12 years) or Adult-Onset RRP (age at diagnosis ≥12 years) will be enrolled.

Inclusion Criteria; Subjects Must:

1. Provide written IRB-approved informed consent in accordance with institutional guidelines;
2. Be ≥18 years of age on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Have histologically documented HPV-6- and/or HPV-11-positive respiratory papilloma or documentation of low-risk positive HPV using a Sponsor approved HPV-6/11 type-specific assay;
4. Have a requirement for frequent RRP intervention in order to remove or resect respiratory papilloma, as defined as at least two RRP surgical (including laser) interventions in the year prior to and including Day 0;
5. Must be appropriate candidate for upcoming surgical intervention per investigator judgement and RRP Staging Assessment score (see Section 6.4.5);
6. Have adequate bone marrow, hepatic, and renal function as defined by: ANC (Absolute Neutrophil Count) ≥1000 cells/mm^3, platelets ≥50,000/mm^3, hemoglobin ≥9 g/dL; concentrations of total serum bilirubin within 1.5 x upper limit of normal (ULN), AST and ALT within 1.5 x ULN, serum creatinine ≤ 1.5 x ULN;
7. Agree that during the trial, male participants will not father a child, and female participants cannot be or become pregnant if they are of child-bearing potential. Subjects must meet one of the below requirements:

a. Be of non-childbearing potential (≥12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone [FSH], if not on hormone replacement);

b. Be surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females);

c. Agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

d. Agree to abstinence from penile-vaginal intercourse, when this is the subject's preferred and usual lifestyle.

Exclusion Criteria; Subjects Must Not:

1. Receive therapy directed towards RRP disease (other than surgery or ablation) including but not limited to anti-virals (including cidofovir), radiation, chemotherapy, anti-angiogenic therapy (including bevacizumab), prophylactic HPV vaccination (including Gardasil) as therapeutic intervention, or therapy with an experimental agent within 3 months prior to Day 0;
2. Have ongoing or recent (within one year) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that requires only hormone replacement, or psoriasis that does not require systemic treatment;
3. Have a diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, including systemic corticosteroids;
4. Have a high risk of bleeding or require the use of anti-coagulants for management of a known bleeding diathesis;
5. Receive any live virus vaccine within 4 weeks prior to first dose of trial treatment or any non-live vaccine within two weeks prior to the first dose of trial treatment;
6. Have a history of clinically significant, medically unstable disease which, in the judgment of the Investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results. This may include chronic renal failure; myocardial ischemia or infarction; New York Heart Association (NYHA) class III/ IV cardiac disease); any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White; cardiomyopathy, or clinically significant arrhythmias); current malignancy with the exception of treated basal or squamous cell skin cancers, prostate cancer, or carcinoma of the cervix in situ; HIV, which may impact the ability to mount an immune response to the study therapy; or drug or alcohol dependence;
7. Have fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
    b. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
    c. Metal implants or implantable medical device within the intended treatment site;
8. Be imprisoned, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

9. Be pregnant or currently breastfeeding; 10. As determined by the Investigator, have any medical or psychological or non-medical condition that might interfere with the subject's ability to participate or affect the safety of the subject.
Clinical Trial Treatment: Subjects will receive a 1 mL injection of INO-3107 IM followed by EP. Doses will be administered at Day 0, Weeks 3, 6, and 9.
[redacted] Device: CELLECTRA® 2000.

SCHEDULE OF EVENTS

Schedule of Events	Screening	Day 0	Week 3 (±4 days)	Week 6 (±4 days)	Week 9 (±4 days)	Week 11 (±1 week)	Week 26 (±2 week)	Week 52 /End of study (±2 weeks)
Informed consent	X							
Medical history, smoking history	X							
Inclusion/Exclusion criteria	X	X						
Demographics	X							
Concomitant medications, AEs	X	X	X	X	X	X	X	X
Physical exam[a]	X	X	X	X	X		X	X
Vital signs	X	X	X	X	X		X	X
Height, weight, BMI		X	X	X	X			
Safety labs[b]	X	X	X	X	X			
Pregnancy test, if applicable[c]	X	X	X	X	X			
INO-3107		X	X	X	X			
Immunology samples	X	X		X	X	X	X	X
Virology sample[d]		X		X		X	X	X
Laryngoscopy and Staging assessment[e]	X[f]			X		X	X	X
Tissue sample[g]	X							X

a. Full physical examination (PE) mandatory at screening and study discharge (Week 52/End of Study visit or relapse), otherwise targeted physical assessment as determined by the Investigator or per subject complaints.
b. Collected within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing.
c. For women of childbearing potential, a negative serum pregnancy test is required at screening and a negative spot urine pregnancy test is required prior to each study treatment.
d. [redacted]
e. Staging assessment to be performed during each laryngoscopy and prior to any RRP intervention using the RRP Staging Assessment tool. Video/photographic documentation of laryngoscopy is required.
f. Staging to be performed prior to Routine RRP intervention at Screening, followed by dosing within 14 days.
g. Biopsy tissue should be sent for HPV typing and immunological evaluation at Screening, Week 52, and at any tissue resection, if applicable. Archival tissue collected within 1 year of Day 0 may be sent at screening. Biopsy required with laryngoscopy at Week 52.

1.0 INTRODUCTION

1.1 BACKGROUND AND SCIENTIFIC RATIONALE: RRP

Human papilloma virus (HPV)-associated malignancies are an emerging global epidemic [1]. The role of HPV-6 and -11 in the etiology of recurrent respiratory papillomatosis (RRP), the most common benign tumor(s) of the laryngeal epithelium, is well-established [2, 3]. RRP is rare, with an incidences estimated at 1.8 per 100,000 adults in the United States [4], and age of diagnosis ranging from young children to older adults. Although most lesions are benign, some undergo malignant transformation, and patients with RRP have a higher risk of developing laryngeal carcinomas [5].

HPV-6 and -11 RRP-associated lesions can occur in the oropharynx, larynx, and upper respiratory tract and the clinical course of RRP varies amongst affected individuals. Selection of treatment, including active monitoring without treatment, surgery, adjuvant therapy, or a combination, depends on clinical history and expected clinical course. Repeated surgical removal of papillomas for symptomatic management remains the mainstay of treatment and results in significant morbidity considering the number of surgical procedures required, impact on voice, effects of repetitive anesthesia, psychological impact, etc [6]. Rarely, malignant transformation may occur, which is usually associated with a dismal prognosis. A few such patients with malignant disease may be candidates for salvage therapies, including potentially definitive surgery [7, 8]. Selected patients in this setting may benefit from radiation although the morbidity of this approach is substantial [8]. Recently, a Phase 2 study of pembrolizumab in patients with RRP demonstrated a response rate of 43%, and this observation supports a rationale for immunotherapeutic management of RRP [9].

Current treatment of HPV-6- and HPV-11-related RRP could potentially be improved or replaced with the addition of HPV-specific immunotherapy. Available preventive HPV vaccines can generate neutralizing antibodies against the HPV major capsid protein L1, but they have not demonstrated therapeutic effects on HPV infection or existing lesions, and are unlikely to engender a cytolytic T-cell response [10]. HPV-specific immunotherapy targeting E6 and E7 proteins, on the other hand, may have therapeutic potential to eliminate preexisting lesions and infections by generating immunity against the HPV virus itself and HPV infected cells. HPV E6 and E7 oncoproteins represent ideal targets for this type of therapeutic intervention because of their constitutive expression in HPV associated tumors and their crucial role in the induction and maintenance of HPV associated diseases [10].

Preclinical studies of INO-3106, a synthetic DNA plasmid encoding versions of the E6 and E7 proteins of HPV-6, have demonstrated strong and specific immune response in animal models [10]. HPV-16/18-specific therapy (VGX-3100) designed and evaluated based on the same synthetic consensus platform, has demonstrated cellular immune responses that correlated with clinical benefit in the form of dysplastic lesion regression and elimination of HPV-16/18 infection in a Phase 2 study, and now support late-phase ongoing clinical trials targeting HPV-16 and HPV-18 associated diseases [11].

A pilot clinical study was conducted in three subjects with HPV-6-associated papillomatosis (HPV-006), treated with INO-3106, and was deemed tolerable. Importantly, INO-3106 was able to demonstrate immunogenicity against HPV-6 E6 and E7 proteins, and evidence of clinical benefit, in two of the three patients treated. Two patients with RRP who previously required every six-month debridement of their RRP

lesions, extended their intersurgical times in a meaningful way; one patient sustaining a surgery-free interval for over 900 days, and another for over 500 days, following therapy with INO-3106 on-study [12]. Following on this study, Inovio is conducting a study of INO-3107, comprised of a single plasmid that encodes for both HPV-6 and HPV-11 E6 an E7 proteins, plus a single plasmid that encodes for IL-12. Inovio is conducting this study in adults with RRP who are at risk of requiring additional and continuous surgery to manage their disease. It is hypothesized that INO-3107 will be safe, tolerable, immunogenic and efficacious in the treatment of patients with HPV-6 and/or HPV-11-associated RRP.

1.2 BACKGROUND INFORMATION: DNA AND ELECTROPORATION WITH CELLECTRA® 2000

Synthetic DNA (sDNA) represents a novel approach for immunotherapy, and offers several potential advantages over current immunotherapies [13]. First, potent T-cell immune responses can be generated to virtually any antigenic sequence. Second, sDNA-based therapies do not include any biological pathogen and therefore cannot revert to a virulent form as opposed to viral- or bacterial-based vaccines, which may mutate back to a virulent form or spread to unintended individuals. Toxicology studies have found no evidence of genome integration from sDNA vaccines [14, 15]. Third, repeated dosing of sDNA therapies is not hindered by neutralization from neutralizing antibodies that target for example viral vector sequences, resulting in decreased or no immunogenicity from these viral-based vaccines. Thus, sDNA therapy allows repeated dosing (or boosting) to potentially increase or maintain immunogenicity over long periods of time. Finally, sDNA therapies are relatively easy to manufacture in large quantities and are generally temperature-stable for long periods of time. Prior work by Inovio on DNA vaccines for HPV-specific therapy has demonstrated promising preliminary results that support late-phase clinical trials targeting HPV 16 and 18 associated diseases and cancers [11].

This study will utilize Inovio's INO-3107 drug product. [redacted] INO-3107 is given IM, followed by EP.

Preclinical studies have shown that the immunogenicity of DNA therapies can be substantially increased by the use of cytokine adjuvants [16-20]. Importantly, the concomitant injection of a plasmid encoding for the human IL-12 cytokine has been shown to enhance sDNA therapy-mediated immunogenicity in humans when delivered using the CELLECTRA® 2000 EP device [21, 22]. We have established in multiple clinical studies targeting both IM and intradermal (ID) delivery that sDNA delivered with the CELLECTRA® 2000 device is a reproducible method of generating immunity in humans for various potential clinical indications ranging from the treatment of cancer to the induction of pathogen prophylaxis [1, 11, 21-27].

Electroporation has repeatedly shown to be an efficient way to introduce DNA into cells [28, 29]. The mechanism of EP is to create a transient electric field that induces temporary and reversible pores in the cell membrane, allowing DNA plasmids to enter the cells. This technology has been used for more than three decades by molecular biologists for cell transfection but in the treatment of human diseases, EP remains experimental in the clinic. Clinical applications of EP have been tested in treatment of cancer and for gene therapy [30-32]. The CELLECTRA® 2000 EP device to be used in this study has been used in several clinical trials, demonstrating a tolerable safety prolife and improved efficacy of DNA transfection (see Section 1.4).

[redacted]

This clinical trial will be conducted in compliance with the clinical study protocol, Good Clinical Practice, and applicable regulatory requirements.

1.3 RATIONALE

Inovio's sDNA therapy VGX-3100 has demonstrated tolerability, immunogenicity and efficacy in a randomized Phase 2b study in HPV-16/18 pre-malignant disease of the cervix, and a pilot study of INO-3106 with INO-9012 in three patients with HPV-6-related aerodigestive disease which demonstrated tolerability, immunogenicity and preliminary efficacy, specifically in two patients with RRP. RRP, although rare, continues to be diagnosed in adults and adolescents, and in children. Therapeutic treatment consists of frequently recurring surgery, and there are few other therapies currently in development. Historical or ongoing clinical studies include evaluating anti-virals (cidofovir), angiogenesis inhibitors (bevacizumab), and checkpoint inhibitors (pembrolizumab, others), and those have shown some promising results [2]. However, no product has been labeled for RRP. INO-3107 has the potential to generate robust T cell responses against HPV-6 and HPV-11 E6 and E7, resulting in eradication of RRP lesions and ideally, eradication of HPV-6 or HPV-11, in patients treated with INO-3107. This study will assess the safety and tolerability, immunogenicity, and efficacy of INO-3107 in adults with RRP.

This study will utilize the dose and schedule previously used in the Inovio HPV-006 study of INO-3106 and INO-9012, in which 6 mg of INO-3106 was given IM followed by EP every three weeks for four doses. In this study, 6.25 mg of INO-3107 will be given every three weeks for four doses. Subjects will be required to have demonstrated a prior history of requiring surgical intervention to manage their RRP, and follow-up will assess safety, tolerability, immunogenicity and the frequency of RRP surgical interventions post Day 0 compared to pre-dose. Patients will be followed for approximately 12 months after the first dose.

1.4 POTENTIAL BENEFITS AND RISKS

INO-3107 has the potential to treat patients with HPV-6 and/or HPV-11-associated RRP, reducing the number of surgical interventions required to control the disease, and potentially to eradicate the virus in treated patients, potentially resulting in a disease cure. This not only would reduce exposure to future inevitable surgical intervention but would also remove the signs and symptoms associated with RRP and the potential for malignant transformation and development of HPV-6- or HPV-11-associated cancer.

The risks associated with DNA therapy have been well described and are coupled with the risks of EP with the CELLECTRA® 2000 device. Over 6000 injections have been delivered and over 2000 subjects have received injections with the Inovio platform utilizing the CELLECTRA® 2000 device to date. In general, the risks associated with DNA therapy and the CELLECTRA® 2000 device are limited to localized injection reactions, including injection site pain, erythema, edema or bruising; fever, fatigue, headache, myalgia, and arthralgia have also been reported. Pain associated with the CELLECTRA® device has been well-characterized and is largely transient [33].

2.0 OBJECTIVES AND PURPOSE

This is a Phase 1/2 open-label, multicenter trial to evaluate the safety, tolerability, immunogenicity, and efficacy of INO-3107 in subjects with RRP.

2.1 HYPOTHESIS

INO-3107, [redacted] delivered intramuscularly (IM) followed by electroporation (EP) with CELLECTRA® 2000 will be generally safe and well-tolerated in subjects with recurrent respiratory papillomatosis secondary to HPV-6 and/or HPV-11.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is a Phase 1/2 open-label, multicenter trial to evaluate the safety, tolerability, immunogenicity, and efficacy of INO-3107 in subjects with RRP. INO-3107 will be administered IM followed by EP in subjects at Day 0, Weeks 3, 6, and 9. Approximately 20 subjects will receive INO-3107 via standard needle, followed by approximately 10 subjects who will receive INO-3107 via the Side Port Needle.

This trial will enroll approximately 30 adults (≥18 years old) who have been diagnosed with either Juvenile-Onset RRP (J-O RRP) as defined by age at first diagnosis <12 years or Adult-Onset RRP (A-O RRP) as defined by age at first diagnosis ≥12 years.

This study will have a safety-run in:

Up to six, subjects will be enrolled with a one week waiting period between each enrolled subject. Each subject will be assessed up to Week 6. Once the first three subjects of up to these six have completed Week 6 assessments, in the absence of dose-limiting toxicity (DLT), subject enrollment may begin in full after review of safety date and discussion between the Sponsor's Medical Monitor and the Investigator's at the subjects' site. However, if prior to the first three to six subjects completing Week 6, a single subject from the first six experiences a DLT then enrollment will be limited to six subjects until all six subjects have reached Week 6 and are assessed for DLT.

If a second subject within the first 6 experiences a DLT within the first 6 weeks, enrollment will stop, and the Sponsor's Medical Monitor and Investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to cease further enrollment. If a change to the protocol is required, enrollment will only be re-initiated after amendment of the protocol and approval of the amended protocol by the respective study IRBs.

Enrollment will continue until approximately 30 subjects are enrolled.

Safety and tolerability will continue to be assessed throughout the study after tolerability has been established in the first six subjects. If more than two subjects experience a DLT at any time during the study, after the initial six subjects are enrolled, the Sponsor will pause enrollment until further discussion with the site Investigator determines that the study may reopen to enrollment.

Tolerability will be determined by the reported incidence of dose-limiting toxicity (DLT), which is defined as:

- Treatment-related NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade ≥3 non-hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours, or;

- Treatment-related NCI CTCAE v5.0 Grade ≥3 hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours.

Additionally, enrollment and additional dosing will be paused until Sponsor discussion with the site Investigator determines that enrollment and dosing may continue, if the following CTCAE v5.0 events occur at any time in the study:

- One Grade 4 or 5 related SAE;
- Two Grade 3 related SAEs

Subjects will undergo routine surgical procedure for removal of papilloma(s) during the screening period within 14 days prior to Day 0 dosing (papilloma removal and Day 0 dose may be performed same day if other eligibility criteria have been fulfilled). Biopsy tissue will be collected and sent to [redacted] for evaluation of secondary and exploratory endpoints. Archival tissue (slides or blocks) obtained within one year of the screening window may be used, or a biopsy conducted during routine surgery.

Status of disease during the trial will be monitored by the Investigator during laryngoscopy including documentation with Staging Assessment scores. If at any time during the trial, surgical removal (including laser) of papilloma is clinically indicated per PI judgement, the subject may undergo procedure for papilloma removal but this must be captured on the electronic case report form. Documentation of the Staging Assessment score prior to surgery is required, and explanation for requirement of surgical removal of papilloma must be documented.

Surgical interventions during the trial must be documented to include at a minimum, information about the appearance and location of tissue being removed and instruments used. Video/photographic documentation of laryngoscopy is required.

This trial will not utilize a Data Safety Monitoring Board. This is a single-arm, open-label trial. The Sponsor will have access to unblinded safety and tolerability data during the trial. At a minimum, the Sponsor's Medical Monitor will review reported adverse events quarterly.

3.1 PRIMARY OBJECTIVE

To evaluate the safety and tolerability of INO-3107 in subjects with HPV-6 and/or HPV-11- associated RRP.

3.2 PRIMARY ENDPOINT

Safety and tolerability as assessed by reported adverse events (AE) and serious adverse events (SAE).

3.3 SECONDARY OBJECTIVE(S)

1. To evaluate the efficacy of INO-3107, as determined by the frequency of RRP surgical interventions in the year following the first dose of investigational product, compared to the frequency in the year prior to Day 0.
2. To evaluate the efficacy of INO-3107 as assessed by changes in the RRP Staging Assessment over time.
3. To evaluate the cellular immune response to INO-3107 when given IM, followed by EP.
4. To evaluate the immunogenicity of INO-3107 as assessed by pro-inflammatory and immunosuppressive elements in resected tumor tissue at study entry and, if available, at subsequent tissue resections.

5. [redacted]

3.4 SECONDARY ENDPOINT(S)

1. Number of RRP surgical interventions in the one year following Day 0, compared to the one year prior to Day 0.
2. Changes in Staging Assessment as measured by the RRP Staging Assessment score over time.
3. Antigen-specific cellular immune responses assessed by:
    - IFN-γ secreting cells in peripheral blood mononuclear cells (PBMCs) by ELISpot
    - T cell phenotype and lytic potential in PBMCs by flow cytometry
4. Assessment of pro-inflammatory and immunosuppressive elements in resected tumor tissue, if available.
5. [redacted]

[redacted]

[redacted]

3.7 EFFICACY ASSESSMENT

A detailed medical history will be obtained for each subject which will include documentation of HPV-6 and/or HPV-11 RRP, a list of RRP surgeries and therapies occurring within 3 years prior to screening, and any periods of remission. Subjects must have had at least two surgical RRP interventions (including laser) in the year prior to and including Day 0, to be eligible for the study. Subjects must require RRP intervention at the time of entry into this study and will undergo surgical removal of their papilloma(s) during screening, within 14 days prior to Day 0 dosing, to maximize standardization of baseline staging across subjects.

The efficacy assessment will be based upon the number of RRP surgical interventions in the 52 weeks post Day 0 compared to the number of RRP surgical interventions in

the year prior to Day 0 dosing. RRP surgical interventions include laser therapies. The trial will also evaluate changes in RRP Staging Assessment over time as a secondary endpoint.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety from the time of signing informed consent through Week 52, or the subject's last visit. All adverse events including SAEs, UADEs, and DLTs. Clinically significant changes in laboratory parameters and vital signs from baseline assessments will be assessed.

3.9 IMMUNOGENICITY ASSESSMENT

[redacted]

3.10 VIROLOGIC ASSESSMENT

The trial will evaluate the presence of HPV-6/11 DNA in tissue samples and peripheral blood, prior to and following study treatment, as described.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

1. Provide written IRB-approved informed consent in accordance with institutional guidelines;
2. Be ≥18 years of age on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Have histologically documented HPV-6- or HPV-11-positive respiratory papilloma or documentation of low-risk positive HPV using a Sponsor approved HPV-6/11 type-specific assay;
4. Have a requirement for frequent RRP intervention in order to remove or resect respiratory papilloma, as defined as at least two RRP surgical (including laser) interventions in the year prior to and including Day 0;
5. Must be appropriate candidate for upcoming surgical intervention per investigator judgement and RRP Staging Assessment score (see Section 6.4.5);
6. Have adequate bone marrow, hepatic, and renal function as defined by: ANC (Absolute Neutrophil Count) ≥1000 cells/mm^3, platelets ≥50,000/mm^3, hemoglobin ≥9 g/dL; concentrations of total serum bilirubin within 1.5 x upper limit of normal (ULN), AST and ALT within 1.5 x ULN, serum creatinine ≤ 1.5 x ULN;
7. Agree that during the trial, male participants will not father a child, and female participants cannot be or become pregnant if they are of child-bearing potential. Subjects must meet one of the below requirements:

a. Be of non-childbearing potential (≥12 months of non-therapy-induced amenorrhea, confirmed by follicle stimulating hormone [FSH], if not on hormone replacement;

b. Be surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females);

c. Agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

d. Agree to abstinence from penile-vaginal intercourse, when this is the subject's preferred and usual lifestyle.

4.2 EXCLUSION CRITERIA

Subjects Must Not:

1. Receive therapy directed towards RRP disease (other than surgery or ablation) including but not limited to anti-virals (including cidofovir), radiation, chemotherapy, anti-angiogenic therapy (including bevacizumab), prophylactic HPV vaccination (including Gardasil) as therapeutic intervention, or therapy with an experimental agent within 3 months prior to Day 0;
2. Have ongoing or recent (within one year) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that requires only hormone replacement, or psoriasis that does not require systemic treatment;
3. Have a diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, including systemic corticosteroids;
4. Have a high risk of bleeding or require the use of anti-coagulants for management of a known bleeding diathesis;
5. Receive any live virus vaccine within 4 weeks prior to first dose of trial treatment or any non-live vaccine within two weeks prior to the first dose of trial treatment;
6. Have a history of clinically significant, medically unstable disease which, in the judgment of the Investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results. This may include chronic renal failure; myocardial ischemia or infarction; New York Heart Association (NYHA) class III/ IV cardiac disease); any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White; cardiomyopathy, or clinically significant arrhythmias); current malignancy with the exception of treated basal or squamous cell skin cancers, prostate cancer, or carcinoma of the cervix in situ; HIV, which may impact the ability to mount an immune response to the study therapy; or drug or alcohol dependence;
7. Have fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;

b. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

c. Metal implants or implantable medical device within the intended treatment site;

8. Be imprisoned, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

9. Be pregnant or current breastfeeding;

10. As determined by the Investigator, have any medical or psychological or non-medical condition that might interfere with the subject's ability to participate or affect the safety of the subject.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

A subject will be considered to have completed the trial when the subject has completed all study visits through Week 52. Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, the Investigator or the Sponsor has the right to discontinue a subject from the trial at any time.

The Investigator must notify the Sponsor within 24 hours when a subject has been discontinued/withdrawn due to an Adverse Event (AE). Any AEs and/or SAEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 7.1: Safety Parameters.

4.3.1 CRITERIA FOR DISCONTINUATION OF INVESTIGATIONAL PRODUCT

A subject should not receive any further investigational product (IP) if any of the following occur:

- Subject withdrawal of consent or subject is lost to follow up
- An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing of any trial medication
- Pregnancy
- Subject non-compliance that, in the opinion of the Investigator or Sponsor, warrants discontinuation
- Initiation of new contraindicated therapy

In the absence of any of the above criterion, if limited clinical benefit is suspected at any time, IP may be discontinued after consultation between the Investigator and the Medical Monitor.

4.3.2 CRITERIA FOR DISCONTINUATION FROM THE STUDY

All subjects should be encouraged to complete all study treatments and follow up visits. If a subject is discontinued from treatment, the subject should be encouraged to stay in the study and complete all follow-up visits and procedures and have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events (Table 1). At a minimum, the Investigator should request to have the subject complete the End of Study visit assessments as indicated in the schedule of events at the subject's final visit.

5.0 CLINICAL TRIAL TREATMENT

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-3107

Investigational product (IP) is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

INO-3107 is the IP to be used in this study. [redacted]

[redacted]

5.1.2 CELLECTRA® 2000

The CELLECTRA® 2000 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 indicated injected plasmid DNA formulation can be introduced into the cells.

The CELLECTRA® 2000 device is indicated to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance efficacy. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

5.1.3 SIDE PORT NEEDLE

As noted above, this study will utilize the Side Port Needle in approximately 10 of 30 subjects, [redacted]

[redacted]

5.2 TREATMENT REGIMEN

Subjects will be administered one 6.25 mg injection of INO-3107 IM followed by EP at Day 0, Week 3, Week 6, and Week 9.

5.3 PACKAGING AND LABELING

5.3.1 INO-3107

Each vial of IP will be labeled with a single panel label consistent with the example product label provided in the Investigator's Brochure (IB). All subjects will receive active INO-3107.

5.3.2 CELLECTRA® 2000 AND SIDE PORT NEEDLE

Please see shipping box for shipping documents and contents, and unpacking instructions.

The CELLECTRA® 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA® 2000 User Manual describes all relevant contraindications, hazards, potential risks and adverse effects, interfering substances or devices, warnings, and precautions. The CELLECTRA® 2000 Pulse Generator and IM Applicator have unique serial numbers. Each IM Array has a Lot Number and Expiration Date. Examples of device labels are provided in the Investigator's Brochure (IB).

The CELLECTRA® 2000 device and its components will be shipped directly from the manufacturer to the study site.

Side Port Needles will be provided to the study site and are packaged with the CELLECTRA® 2000 IM Array in a sterile enclosure.

5.4 HANDLING AND STORAGE

5.4.1 INO-3107

[redacted]

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 Preparation and Dispensing

[redacted]

INO-3107 will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee. It is the responsibility of the Investigator to ensure that INO-3107 is only dispensed to study subjects.

[redacted]

Detailed instructions on handling and dispensing of INO-3107 are provided in the Pharmacy Manual.

5.6 Use of Study Device

The instructions for use of the CELLECTRA® 2000 device is provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose.

[redacted]

5.7 Investigational Drug and Study Device Accountability

5.7.1 INO-3107

It is the responsibility of the Investigator to ensure that a current record of IP accountability is maintained at the study site. The IP must have full traceability from the receipt of the product through participant use, disposal or return of the products. Records or logs must comply with applicable regulations and guidelines. The accountability information is provided in the Pharmacy Manual.

5.7.2 CELLECTRA® 2000 Accountability

Each clinical site is responsible for maintaining investigational device accountability. The device must have full traceability from the receipt of the products through participant use, disposal or return of the products. The site must document acknowledgement of receipt and notify Inovio upon receipt of study devices. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. Pulse generator and IM applicator serial numbers, and IM Array lot number. The IM Applicator is intended to be used multiple times on the same subject and then disposed

after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM Applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable Array must be discarded after use in accordance with institutional policy for disposal of sharp needles/instruments.

Site personnel will be requested to download EP data and provide to Inovio after each treatment.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-3107

Upon completion or termination of the study, all unused and/or partially used IP must be destroyed at site per institution policy or returned to Inovio Pharmaceuticals, Inc. or its designee, if site cannot destroy IP. If IP is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. Reconciliation of any unused IP must be performed and provided to the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor for review prior to on-site destruction.

The used IP vials will be discarded per site's used IP disposal procedure. It is the Investigator's responsibility to arrange for disposal of all empty vials, 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.

If requested by the Sponsor, the return of unused IP should be arranged by the responsible Inovio Representative or by the authorized site representative if an Inovio representative is not present. All IP returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Inovio Pharmaceuticals, Inc.

5.8.2 CELLECTRA® 2000

Upon completion or termination of dosing, an Inovio Representative will provide instructions regarding the component(s) to be returned to Inovio Pharmaceuticals, Inc., destroyed onsite or shipped to a destruction vendor.

All product returned to Inovio Pharmaceuticals Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by the Inovio Representative. Used IM Arrays should be discarded in the sharp's container immediately after use. The used IM Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio per instructions provided. If the used IM Applicators are destroyed on site, it is the Investigator's responsibility to ensure that:

- Arrangements have been made for disposal;
- Written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee;

- Procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and;
- Appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Trial Schedule of Events in the Clinical Protocol Synopsis summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. A participant will be required to provide informed consent (Section 6.2) prior to any study procedure being performed. Protocol waivers or exemptions will not be granted. Therefore, adherence to the study design and assessments are essential and required for study conduct.

6.1 PROCEDURE BY VISIT

Refer to sections 6.1.1 and 6.1.2 for study procedures and the times at which they are to be carried out.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and their ability to comply with protocol requirements by completing all screening assessments. Subjects' post-menopausal status must meet requirements as specified in the inclusion criteria. The following screening evaluations will be performed within 60 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration.

If a subject does not meet an inclusion or exclusion criterion due to a transient and non-clinically significant event at Screening, relevant Screening evaluations may be repeated within the same 60-day Screening period. If the subject fails twice, they will be considered a screen failure.

• Signed and dated informed consent (Section 6.2);
• Review and confirm all inclusion/exclusion criteria (Section 4.1 and 4.2);
• Obtain and document complete medical history, surgical history (including all past procedures), present conditions and concomitant illnesses (Section 6.1.1.1); document all present and/or new or ongoing adverse events prior to administration of IP;
• Collect demographics (Section 6.1.1.2);
• Smoking history (Section 6.1.1.3);
• Full physical examinations (Section 6.4.1);
• Record current concomitant medications/treatments (Section 6.13);
• Record vital signs heart rate (HR), respiratory rate (RR), blood pressure (BP) and body temperature (Section 6.4.2);
• Record body weight, height and determine BMI (Section 6.4.3);
• Collect blood for screening laboratory evaluations (Section 6.4.4);
• Collect blood for serum pregnancy test, if applicable (Section 6.4.4);
• Collect whole blood and serum for immunology assessment (Section 6.10);
• Perform laryngoscopy and Staging assessment (Section 6.4.5) prior to surgical removal of papilloma(s).
• Surgical removal of papilloma(s)
• Biopsy tissue (archival slides or blocks) obtained within one year of screening, or during surgical removal of papilloma(s) will be collected.

Subjects will undergo routine procedure for removal of papilloma(s) during the screening period, however dosing on Day 0 must be performed within 14 days following the procedure. If other eligibility criteria have been confirmed, Day 0 dosing may be performed the same day immediately following the papilloma removal. The following assessments should be noted at the time of the procedure:

- Record vital signs heart rate (HR), respiratory rate (RR), blood pressure (BP) and body temperature (Section 6.4.2);
- Record current concomitant medications/treatments (Section 6.13);
- Collect any new adverse events.

6.1.1.1 MEDICAL HISTORY

A medical history will be obtained by the Investigator or qualified designee at the time of Screening. Medical history will include all active conditions, past conditions, initial diagnosis date, HPV type (if available), and all prior surgical procedures and therapies directed toward RRP disease including adjuvant therapies, especially those occurring within the 3 years prior to Screening, as well as any periods of disease remission. Illnesses first occurring or detected after the signing of the informed consent, or during the study and/or worsening of an existing illness in severity, frequency or nature after signing of the informed consent are to be documented as AEs on the CRF. All prior treatments should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing or new treatments taken at or after the signing of the informed consent, should be recorded in the CRF as concomitant medications.

6.1.1.2 DEMOGRAPHICS

Demographic information will be collected via self-report (unless note otherwise), including but not limited to age, biological sex and race and ethnicity.

6.1.1.3 SMOKING HISTORY

Smoking history will be collected at Screening via self-report.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject's Day 0 dose will be scheduled within 14 days after the next planned surgical intervention. If timing allows, the Day 0 dose may be given on the same day immediately following the next planned surgical intervention. Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Week 52 visit. All subjects will be followed per assessments outlined below.

6.1.2.1 Day 0

The following evaluations will be performed on Day 0 **prior to IP administration**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Targeted physical examination (Section 6.4.1);
- Record vital signs (Section 6.4.2);
- Record body weight, height and determine BMI (Section 6.4.3);
- Collect urine for urine pregnancy test, if applicable (Section 6.4.4);
- Collect whole blood and serum for immunology assessment (Section 6.10);

- Collect safety labs within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing (Section 6.4.4);

The following evaluations will be performed on Day 0 **after IP administration**:

- Collect any new adverse events;
- Download EP Data (Section 6.5.1).

6.1.2.2 Week 3

The following evaluations will be performed at this visit **prior to IP administration**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Targeted physical examination (Section 6.4.1);
- Record vital signs (Section 6.4.2);
- Record body weight, height and determine BMI (Section 6.4.3);
- Safety labs collected within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing (Section 6.4.4);
- Collect urine for urine pregnancy test, if applicable (Section 6.4.4).

The following evaluations will be performed **after IP administration**:

- Collect any new adverse events;
  Download EP Data (Section 6.5.1).

6.1.2.3 Week 6

The following evaluations will be performed **prior to IP administration**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Targeted physical examination (Section 6.4.1);
- Record vital signs (Section 6.4.2);
- Record body weight, height and determine BMI (Section 6.4.3)
- Safety labs collected within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing (Section 6.4.4).
- Collect urine for urine pregnancy test, if applicable (Section 6.4.4);
- Collect whole blood and serum for immunology assessment (Section 6.10).
- Laryngoscopy and Staging assessment (Section 6.4.5).
  - If it is the Investigator's practice to routinely biopsy during laryngoscopy, this should be performed at this visit.

The following evaluations will be performed **after IP administration**:

- Collect any new adverse events;
- Download EP Data (Section 6.5.1).

6.1.2.4 Week 9

The following evaluations will be performed **prior to IP administration**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);

- Targeted physical examination (Section 6.4.1);
- Record vital signs (Section 6.4.2);
- Record body weight, height and determine BMI (Section 6.4.3)
- Safety labs collected within 72 hours prior to dosing such that results are available and assessed against DLT criteria prior to dosing (Section 6.4.4);
- Collect urine for urine pregnancy test, if applicable (Section 6.4.4);
- Collect whole blood and serum for immunology assessment (Section 6.10).

The following evaluations will be performed **after IP administration**:

- Collect any new adverse events;
- Download EP Data (Section 6.5.1).

6.1.2.5 Week 11

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Collect whole blood and serum for immunology assessment (Section 6.10);
- Laryngoscopy and Staging assessment (Section 6.4.5).
  - If it is the Investigator's practice to routinely biopsy during laryngoscopy, this should be performed at this visit.

6.1.2.6 Week 26

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Targeted physical examination (Section 6.4.1);
- Record vital signs (Section 6.4.2);
- Collect whole blood and serum for immunology assessment (Section 6.10);
- Laryngoscopy and Staging assessment (Section 6.4.5);
- If it is the Investigator's practice to routinely biopsy during laryngoscopy, this should be performed at these visits.

6.1.2.7 Week 52/End of Study visit

The following evaluations will be performed:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.13);
- Full physical examinations (Section 6.4.1);
- Record vital signs (Section 6.4.2).
- Collect whole blood and serum for immunology assessment (Section 6.10).
- Laryngoscopy and Staging assessment (Section 6.4.5).
- Biopsy
  - Tissue will be sent to the study laboratory for HPV genotyping and immuno-assessment

6.2 INFORMED CONSENT

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

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each participant who consents will be assigned a unique subject identification number (SID), which identifies the participant for all trial-related procedures. SIDs are a combination of a four-digit site code and a four-digit participant number starting with 0001. Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date will be documented in the eCRF.

6.4 SAFETY EVALUATIONS

6.4.1 PHYSICAL EXAM AND TARGETED PHYSICAL ASSESSMENTS

A full physical examination will be conducted during Screening and at study discharge (Week 52 or any other study discontinuation visit). A targeted physical assessment will be performed at other visits indicated per schedule of events as determined by the Investigator or directed per participant complaints.

6.4.2 VITAL SIGNS

Vital signs including oral temperature, respiration rate, blood pressure and heart rate will be measured at Screening and all other in-person study visits.

6.4.3 HEIGHT AND WEIGHT

Weight (kg) and height (cm) will be collected at Screening and at each dosing visit in order to calculate BMI.

6.4.4 LABORATORY EVALUATIONS

At Screening and select times during the study, blood samples will be collected for safety assessments. Safety labs will be collected within 72 hours prior to dose such that results are available and assessed against DLT criteria prior to dosing.

Approximately 450 mL of blood will be drawn from each participant over the course of the study for safety and immunology assessments. A description of the immunology assessments can be found in Section 6.10.

Hematology (Complete blood count (CBC) with automated differential):

White blood cell (WBC) count, Red blood cell (RBC) count, hemoglobin, hematocrit and platelet count will be measured at Screening, and prior to dosing at Day 0, Weeks 3, 6, and 9.

- Approximately 2.5 mL of whole blood to be drawn per visit

Serum chemistry:

Electrolytes (Sodium [Na], Potassium [K], Chloride [Cl], Bicarbonate [HCO_3], Calcium [Ca], Phosphate [PO_4]), glucose, BUN (blood urea nitrogen), serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and Creatinine (Cr) will be measured at Screening, and prior to dosing at Day 0, Weeks 3, 6, and 9.

- Approximately 4 mL of whole blood to be drawn per visit

Pregnancy Testing:

For women of childbearing potential (WOCBP), a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed prior to each dose. A negative result for urine β-HCG (test must have a sensitivity of at least 25 mIU/mL) must be available prior to each administration of IP. If the β-HCG test is positive, indicating that the participant is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant participants for the remainder of the study and to determine the outcome of the pregnancy.

- Approximately 0.5 mL of whole blood to be drawn for serum pregnancy test at Screening

6.4.5 LARYNGOSCOPY AND STAGING ASSESSMENT

Laryngoscopy will be performed at Screening (prior to routine removal of papilloma(s)), and at Weeks 6, 11, 26, and 52. If it is the Investigator's practice to routinely biopsy during laryngoscopy, this should be performed at these visits. Biopsy will be performed at Week 52.

The status of disease will be assessed during each laryngoscopy and an RRP Staging Assessment score will be determined using a modified Derkay staging tool [34]. Specific instructions and guidelines will be provided under separate cover.

Subjects will undergo surgery for removal of papilloma(s) during the screening period within 14 days prior to Day 0 dosing (papilloma removal and Day 0 dose may be performed same day if other eligibility criteria have been fulfilled).

Status of disease during the trial will be monitored by the Investigator during laryngoscopy including documentation with Staging Assessment scores. If at any time during the trial, surgical removal (including laser) of papilloma is clinically indicated per PI judgement, the subject may undergo procedure for papilloma removal but this must be captured on the electronic case report form. Documentation of the Staging Assessment score prior to surgery is required, and explanation for requirement of surgical removal of papilloma must be documented.

Surgical interventions during the trial must be documented to include at a minimum, information about the appearance and location of tissue being removed and instruments used. Video/ photographic documentation of laryngoscopy is required. Further instructions will be provided under separate cover.

6.5 INJECTION AND ELECTROPORATION (EP)

Subjects will receive a four-dose series of INO-3107 by IM injection in the deltoid (or anterolateral quadriceps muscle as an alternate option, if deltoid muscle is not possible or appropriate) followed immediately by EP with CELLECTRA® 2000 at Day 0, Week 3, 6, and 9.

Approximately 20 subjects will be administered INO-3107 by standard needle, followed by approximately 10 subjects who will be administered INO-3107 by Side Port Needle.

Study treatment should not be given within 2 cm of a tattoo, keloid or hypertrophic scar. If there is implanted metal, implanted device, within the same limb then use of the deltoid muscle on the same side of the body is excluded.

6.5.1 DOWNLOADING OF EP DATA FROM CELLECTRA® 2000 DEVICE

Following each Study IM Administration, data will be downloaded from the CELLECTRA® 2000 device and the data file that is created should be provided to the Sponsor. Instructions on how to download the data and Sponsor contact information are provided separately. Training will also be provided.

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

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

In case of pain, participants may be treated with a non-narcotic analgesic (e.g.,acetaminophen) after injection/EP.

Participants who are allergic to or have contraindications to EMLA, acetaminophen, or a mild sedative may be offered a suitable alternative.

Medication taken for pain management will be documented as concomitant medications.

6.7 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry and hematology at the visits listed in the Schedule of Events as listed in Section 6.4.4.

Laboratory AEs will be evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Laboratory values that are not clinically significant (NCS) in the Investigator's opinion will not be reported as adverse events.

6.8 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

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

6.9 ASSESSMENT OF INJECTION SITE REACTIONS

The injection site will be assessed by study personnel prior to and at least 30 minutes after each study treatment and at the subsequent study visit following dosing.

When evaluating injection site reactions throughout the study, it is important to be as specific as possible by selecting the most appropriate term and use the grading scale as listed in CTCAE v5.0. Injection site reactions and administration site pain will be evaluated starting 30 minutes following injection/EP and reported as adverse events on the CRF.

6.10 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at baseline (screening and Day 0 prior to dosing) and at Weeks 6, 9, 11, 26 and 52. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

PBMCs will be isolated from whole blood samples. [redacted]

6.11 HPV-6/11 TESTING

Historic HPV-6/11 genotyping results may be used to determine a subject's eligibility for the trial. If historic results are not available, archival tissue collected during previous papilloma removal procedures or biopsy tissue obtained during screening may be used to determine eligibility.

Archival tissue (within 1 year of the screening visit) or biopsy tissue collected at screening, and tissue collected at Week 52, will undergo HPV-6/11 testing at a central laboratory. If tissue is resected or biopsied during the study as clinically indicated, this may also undergo HPV-6/11 testing at a central laboratory.

[redacted]

Details of sample collection and shipment information will be provided in the Laboratory Manual.

6.12 TISSUE IMMUNOGENICITY ASSESSMENT

If there is residual tissue in the paraffin block after HPV genotyping from the tissue collected at screening, Week 52, and as clinically indicated during the course of the study, the block or unstained slides prepared from the block will be collected for the assessment

of pro-inflammatory and immunosuppressive elements and their association with treatment success.

[redacted] Additional markers may be assessed, and the markers listed here may change as new relevant information becomes available.

[redacted]

[redacted]

6.13 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription) taken at the time of Screening and ongoing from signing of the informed consent to study discharge that do not affect a subject's eligibility for participation (see Section 4.2, Exclusion Criteria) must be recorded on the case report forms (CRFs).

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor.

6.14 RESTRICTIONS

Prohibited Concomitant Medications and Treatments

The following medications and treatments are prohibited:

- Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent; use of inhaled (nasal or bronchial), otic and ophthalmic corticosteroids are allowed;
- Disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), and biologic disease modifying drugs such as TNF-α inhibitors (e.g. infliximab, adalimumab or etanercept) at screening and throughout the study;
- Administration of any non-study related, non-live vaccine within 2 weeks of any study treatment or within 4 weeks of any study treatment for any non-study, live vaccine (prophylactic HPV vaccination, including Gardasil) as attempted therapeutic intervention while on-study is not permitted);
- Use of bevacizumab and cidofovir should be stopped at least 3 months prior to Day 0 visit;
- Post-surgical course of anti-inflammatory medication and steroids should be avoided.

Other Restrictions

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

Subjects should refrain from becoming pregnant for the duration of the trial by using appropriate contraceptive measures as (See Inclusion Criteria, Section 4.1). Lapses in contraceptive use should be reported to investigator and/or other study personnel.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-3107 will be measured and graded in accordance with the CTCAE v5.0.

7.2 ADVERSE EVENTS (AEs)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Events (AEs) include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of clinical trial drug)
- Any pre-existing condition, with the exception of the condition under investigation in this study, that increases in severity, or changes in nature during or as a consequence of the clinical trial drug administration phase
- Complications of pregnancy (refer to section 7.11: Reporting Pregnancy During the Clinical Trial)

Adverse Events (AEs) do not include the following:

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

7.3 ADVERSE DRUG REACTION (ADR)

All noxious and unintended responses to a medicinal product related to any dose. This means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

7.4 SERIOUS ADVERSE EVENTS (SAEs)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

- Refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Includes any hospitalization in which the subject has been admitted to the hospital regardless the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE.
- Results in persistent or significant disability/incapacity
  - A substantial disruption of a person's ability to conduct normal life functions (i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life).
- Results in congenital anomaly or birth defect and/or
- An important medical event
  - An event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clarification of Serious Adverse Events (SAEs)

- Death in itself is not an AE. Death is an outcome of an AE, but when the cause of death has not been provided, use the event term: death of unknown cause
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE

7.5 UNEXPECTED ADVERSE DRUG REACTION

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an unapproved investigational product, package insert/summary of product characteristics for an approved product).

7.6 UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

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

A UADE is a type of SAE that requires reporting to the Sponsor in accordance with section 7.9: Safety Data Reporting Period, Method of Collection and Submission.

7.7 DEVICE DEFICIENCY

Please refer to Section 7.12 for more information.

7.8 SAFETY AND TOXICITY MANAGEMENT

The Medical Monitor is responsible for the overall safety monitoring of the clinical trial.

Safety monitoring assessments include but are not limited to:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity and causal relationship to clinical trial IP administration
- Changes in laboratory parameters
- Local and systemic injection site review; special attention will be paid to the examination of the injection site
- Dose Limiting Toxicities (DLT)

7.8.1 Dose Limiting Toxicity (DLT)

For the purpose of this clinical trial, the following are DLTs and are to be reported to the Sponsor in accordance with section 7.9: Safety Data Reporting Period, Method of Collection and Submission.

- ≥Grade 3 non-hematological toxicity (graded per CTCAE v. 5.0) that does not respond to supportive therapy and lasts for longer than 48 hours
- ≥Grade 3 hematological toxicity (graded per CTCAE v. 5.0) that does not respond to supportive therapy and lasts for longer than 48 hours

Refer to Section 3.0 for information about management of DLTs.

7.8.2 Abnormal Laboratory Value

Laboratory results will be evaluated based on the normal ranges and toxicity scale within CTCAE v. 5.0. The PI will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the PI's opinion should not be reported as an adverse event.

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

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of clinical trial treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the PI as clinically significant (CS)

Abnormal laboratory values that meet the criteria of an AE or SAE should be reported in accordance with Section 7.9: Safety Data Reporting Period, Method of Collection and Submission.

7.8.3 Clinical Trial Stopping Rules

Enrollment and additional dosing will be paused until Sponsor discussion with the site Investigator determines that enrollment and dosing may continue, if the following CTCAE v5.0 events occur at any time in the study:

- One Grade 4 or 5 related SAE;
- Two Grade 3 related SAEs

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time when informed consent is obtained to Week 52 or at participant's last visit due to early discontinuation. This information will be captured in the Electronic Data Capture (EDC) system.

If the PI determines that the AE meets serious criteria, then the AE will be recorded as an SAE.

SAEs and DLTs will be reported to the Sponsor from the time the subject signs the informed consent until Week 52 or at participant's last visit due to early discontinuation.

All SAEs (regardless of causal relationship) and DLTs, will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. [redacted]

The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the EDC.

For the events that are considered a DLT, the PI will contact the Sponsor within 24 hours of becoming aware of the event to discuss whether dosing should continue.

SAE Contact Information

Safety Email: [redacted]
Safety Fax: [redacted]
Safety Phone: [redacted]

Medical Monitor Direct contact Information

Medical Monitor: Jeffrey Skolnik, M.D.
Email: [redacted]
Cell Phone: [redacted]

All SAEs, and DLTs must be followed by the PI until resolution or return to baseline status, or stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period.

Follow-up information is to be submitted to the Sponsor on an SAE Report Form and within 24 hours of becoming aware of the information.

If medical records are submitted to the Sponsor with the SAE Report Form, the clinical trial site must:

- Redact the medical records of all personal data (e.g., confidential subject data, Personal Identifying Information (PII)
- Provide the assigned clinical trial subject number (SID) on the records

7.10 ADVERSE EVENT REPORTING

This section provides details on reporting the safety information.

7.10.1 Submitting the Initial Serious Adverse Event (SAE) Report Form

The PI should include as much safety information as possible when submitting the initial report, but the report must include the following at a minimum:

- The Adverse Event
- The subject's assigned identification (SID) number
- Investigational product(s) (IP) and/or device
- Investigator Causal Relationship to the IP(s) and/or device
- Serious criteria
- Reporter name and contact information

If a case is submitted to the Sponsor with only the "minimum" information, a more detailed or updated follow-up report will be sent to the Sponsor as soon as possible but no later than three (3) calendar days after the date of the initial report.

7.10.2 Recording the Event

Principal Investigators (PIs) should use correct medical terminology/concepts when recording adverse events on the EDC and Safety Report Form. The use of colloquialisms and abbreviations should be avoided.

A medical diagnosis, if known, should be recorded rather than individual signs and symptoms. However, if the signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual sign and/or symptom should be recorded. If a diagnosis is subsequently established, all previously signs and/or symptoms will be nullified and replaced with a single medical diagnosis.

7.10.3 Assessing Severity (Intensity)

Severity is used to describe the intensity of a specific event (e.g., mild, moderate, severe).

The PI will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v5.0.

7.10.4 Causal Relationship of Clinical Material to Adverse Events (AEs)

A causally related AE is one judged to have a possible, probable or definite relationship to the administration of the IP and/or the study device. An AE may also be assessed as not related to the IP and/or the study device. Because the PI is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the PI is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The PI is aware of the subject's clinical state and may have observed the event, and thus may be

sensitive to distinctions between events due to the underlying disease process versus events that may be product-related.

Principal Investigators (PIs) should use their knowledge of the clinical trial subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the IP and/or the study device and the causal relationship reported as "Yes" or "No" accordingly. Causality should be assessed by the PI as related to drug, related to device, or related to both drug and device (i.e., related to both or indiscernible) by the following criteria:

- Yes - there is a reasonable possibility that administration of the clinical trial treatment (drug or device or both drug and device) contributed to the event
- No - there is no reasonable possibility that administration of the clinical trial treatment contributed to the event and there are more likely causes

The following guidance should also be taken into consideration:

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

The rationale for the PI's causal assessment is to be recorded on the SAE Report Form.

The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory authority(ies).

7.11 Reporting Pregnancy During the Clinical Trial

Subjects who are pregnant or expect to become pregnant during the course of the clinical trial will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through the study completion (last visit) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after enrolling in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the PI and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

The PI will report this event to their IRB/REB/EC in accordance with their policies and procedures.

The clinical trial site must request the subject's permission to query pregnancy outcome and follow the subject for outcome of the pregnancy. The subject will continue to be followed for safety assessments without receiving additional IP until clinical trial discharge in accordance with this protocol. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. The PI should use clinical judgment regarding subsequent clinical trial-related blood collection based on the presence or absence of anemia in each subject.

Male subjects will be instructed through the ICF to immediately inform the PI if their partner becomes pregnant until study completion (last visit). A Pregnancy Form will be completed by the PI and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the PI will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The PI will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If a PI is contacted by the male subject or his pregnant partner, the PI may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

If the end of the pregnancy occurs after the clinical trial has been completed, the outcome will be reported directly to the Sponsor.

7.12 REPORTING DEVICE-RELATED COMPLAINTS OR DEFICIENCIES

All product complaints that meet the definition of device deficiency must be reported to the Sponsor within 10 days of discovery, with the exception of SAEs which require 24-hour reporting. The error reporting or complaint form must be completed and emailed to the Sponsor at [redacted]

Device deficiencies include malfunctions, use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled.

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

7.13 NOTIFYING REGULATORY AUTHORITIES AND INSTITUTIONAL REVIEW BOARDS (IRBS)/ETHICS COMMITTEES (ECS) OF SAFETY INFORMATION

7.13.1 Sponsor Responsibilities

- Determine whether the safety information meets the requirements for expedited reporting to the applicable regulatory authorities
- Prepare and submit the safety report to the applicable regulatory authorities
- Send all participating PIs a safety report and Investigator Safety Letter (i.e., Dear Investigator Letter) that will include a statement if there is or is not any significant new safety information that might influence the risk-benefit assessment of the IP and/or study device, sufficient to consider changes in product administration or overall conduct of the clinical investigation

7.13.2 Principal Investigator (PI) Responsibilities

- Forward a copy of the safety report and Investigator Safety Letter (i.e., Dear Investigator Letter) to their IRB/REB/EC as soon as practical in accordance with the governing policy and/or procedures
- Notify their IRB/REB/EC of safety information (i.e., SAEs, pregnancies, etc.) that occur at their clinical trial site in accordance with their local institutional policy

7.14 POST-TRIAL REPORTING REQUIREMENTS

Principal Investigators (PIs) are not obligated to actively seek AEs or SAEs beyond the clinical trial reporting period. However, if the PI becomes aware of an AE or SAE that occurs after the Completion or Termination Visit and the event is deemed by the PI to be probably or possibly related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.15 CLINICAL TRIAL DISCONTINUATION

The Sponsor reserves the right to discontinue the clinical trial at this site or at multiple sites for safety or administrative reasons at any time. In particular, a clinical trial site that does not recruit at a reasonable rate may be discontinued. Additionally, the clinical trial may be discontinued at any time by an IRB/REB/EC, the Sponsor, or a regulatory authority as part of their duties to ensure that clinical trial subjects are protected.

If the clinical trial is discontinued and/or the clinical trial site closed for any reason, an Inovio Representative will provide instructions regarding which device components should be returned to Inovio Pharmaceuticals, Inc., destroyed onsite and/or shipped to a destruction vendor. The PI should ensure that their site file documents are complete prior to archiving and provide copies of any requested documents to the Sponsor for its Trial Master File (TMF).

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The Statistical Analysis Plan is contained in the sections that follow.

8.2 GENERAL CONSIDERATIONS

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

This is a single-arm, multi-center clinical trial in subjects with HPV-6- and/or HPV-11-associated recurrent respiratory papillomatosis (RRP). The primary objective is to evaluate safety. The primary endpoint is safety and tolerability as assessed by reported adverse events (AE) and serious adverse events (SAE). Secondary efficacy analyses include evaluation of frequency of RRP surgical interventions in the year following the first dose of investigational product, compared to the frequency in the year prior to Day 0 dosing, and changes in RRP Staging Assessment over time. Other secondary analyses concern cellular immunological measures, and tissue immunological measures. [redacted] All safety, efficacy, and immunogenicity data will be analyzed separately and combined for patients administered INO-3107 by needle type.

8.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis will be tested in this study.

8.4 ANALYTICAL POPULATIONS

The analysis populations will be the following.

The intention to treat (ITT) population includes all subjects who are eligible.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of INO-3107.

The per-protocol (PP) population comprises subjects who receive all doses of INO-3107 and have no protocol violations. Subjects excluded from the PP population will be identified and documented prior to locking of the trial database.

The safety analysis set includes all subjects who receive at least one dose of INO-3107.

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 Primary Analyses

The primary analyses for this trial are safety analyses of Treatment Emergent Adverse Events (TEAE) and clinically significant changes in safety laboratory parameters from baseline.

TEAEs are defined for this trial as any AEs that occur following Day 0 following administration of study drug (IM + EP), until 30 days following the last dose. All TEAEs will be summarized among the Safety Population by frequency. These frequencies will be presented overall, by system organ class and by preferred term, the percentage of subjects affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to study treatment. Multiple occurrences of the same

AE will be counted only once following a worst-case approach with respect to severity and relationship to study treatment. All serious TEAEs will also be summarized as above.

The main summary of safety data will be based on TEAEs. For this summary, the frequency of preferred term events will be calculated along with 95% confidence intervals, using the exact method of Clopper-Pearson. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred. AEs and SAEs that are not TEAEs or serious TEAEs will be presented in listings.

For AE data, partial start dates will be imputed to the date of treatment to conservatively report the event as treatment-emergent, whenever the portion of the date is consistent with that of the study treatment. Otherwise, it will be imputed to the earliest date consistent with the partial date. A completely missing onset date will be imputed as the day of treatment. Partial stop dates will be assumed to be the latest possible day consistent with the partial date.

AE duration will be calculated as (Stop Date – Start Date) + 1.

Laboratory response variables will be descriptively summarized per time point and as changes from baseline including 95% confidence intervals. Shifts from baseline according to the CTCAE will also be presented. Laboratory values considered clinically significant will be presented in listings.

All of the safety analyses will be conducted on the subjects in the safety analysis set.

Analyses will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.2 Secondary Analyses

8.5.2.1 EFFICACY

The frequency of RRP surgical interventions in the year following the first dose of investigational product, compared to the frequency in the year prior to Day 0 dosing, will be summarized descriptively using mean fold-change and a 95% t-distribution-based CI.

Changes in RRP Staging Assessment scores from baseline pre-dose to each post-dose evaluation will be analyzed. Median changes and associated 95% confidence intervals will be computed.

The relationship between the efficacy endpoint versus miRNA results will be examined. Relationships will be examined by using regression models, which model the endpoint outcome versus miRNA results as regressor variables.

Intersurgical intervals will also be summarized.

Analyses will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall. Efficacy analysis using the mITT population will be conducted. The PP population will also be used for a supportive analysis.

8.5.2.2 IMMUNOGENICITY

Increases from baseline in interferon-γ ELISpot and flow response magnitudes will be summarized. The median increases and associated 95% confidence intervals will be calculated.

Changes from baseline in tumor tissue response magnitudes will be summarized. The mean increases and associated 95% t-distribution based confidence intervals will be calculated.

Valid samples for statistical analysis purposes will be those collected within 7 days of the specified visit. Baseline is defined as the last measurement prior to the first treatment administration.

The mITT population will be used for immunogenicity analyses.

Analysies will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.3 Disposition

Disposition will be summarized and will include the number and percentage eligible, the number and percentage who received each dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.
Analysis will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.4 Demographic and Other Baseline Characteristics

8.5.4.1 DEMOGRAPHICS

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

Analysis will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.4.2 PRIOR MEDICATION

Prior medications are those that were used before the start of the trial (prior to Day 0). Partial stop dates of prior medications will be assumed to be the latest possible date consistent with the partial date; start dates will not be imputed. Data for all prior medications will be summarized with percentages for the mITT population.

Analyses will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.5 Interim Analyses

No formal interim analyses will be performed for this study.

8.5.6 Multiplicity

Not applicable.

8.5.7 Missing Values

All analyses will be based upon observed data.

8.5.8 Exploratory Analyses

8.5.8.1 [redacted]

[redacted]

8.5.8.2 [redacted]

[redacted]

8.5.8.3 CONCOMITANT MEDICATION

Concomitant medications are those used during the course of the trial (on or after Day 0). Partial stop dates of concomitant medications will be assumed to be the latest possible date consistent with the partial date; start dates will not be imputed. Data for all concomitant medications will be summarized with percentages, for the mITT population.

Analysis will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.5.8.4 Vital Signs

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

Analysis will be summarized and presented by number of prior surgical interventions (≤2, 3-5, and ≥6) and overall.

8.6 SAMPLE SIZE/POWER

No formal power analysis is applicable to this study, as descriptive statistics will be used to summarize the data.

For 30 INO-3107 administered subjects, the trial provides 95% confidence that the true incidence of SAEs is <12% if no SAEs are observed.

8.7 RANDOMIZATION AND BLINDING

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

9 ETHICS

9.1 INVESTIGATOR AND SPONSOR RESPONSIBILITIES

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

9.2 INSTITUTIONAL REVIEW BOARD (IRB)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the Institutional Review Board (IRB) and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IRB include the following:

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

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each participant prior to enrollment into the trial, and/or from the participant's legally authorized representative. The process for obtaining informed consent must also be documented in the participant's medical record. (Also refer to section 6.2.)

9.3.2 Compliance with IRB Requirements

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

9.3.3 Compliance with Good Clinical Practice

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

9.3.4 Compliance with Electronic Records/Signatures Regulations

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

9.3.5 Compliance with Protocol

Participants are not required to follow special instructions specific to the IP used in this trial. Participants will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting participant safety must be reported to the Medical Monitor immediately.

9.3.6 Changes to the Protocol

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to trial participants, or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers). While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting participant safety must be reported to the Medical Monitor immediately.

9.3.7 Vulnerable Subjects

This study prohibits the enrollment of subjects who are imprisoned, or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness, as well as of children.

10 DATA COLLECTION, MONITORING AND REPORTING

10.1 CONFIDENTIALITY AND PRIVACY

A report of the results of this clinical trial may be published or sent to the appropriate regulatory authorities in any country in which the clinical trial products are legally marketed or may ultimately be marketed, but the subject's name/identity will not be disclosed in these documents. The clinical trial Sponsor, its agents, the IRB/REB/EC and regulatory authorities will have direct access to the subject's medical records for the purposes of trial-related monitoring, auditing and inspection. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation are to be obtained from each subject, and/or from the subject's legally authorized representative, prior to enrollment in the clinical trial, in accordance with all applicable laws, regulations and/or directives relating to privacy and data protection.

11 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical trial. Source data are contained in original source documents.

Examples of original source documents and data records include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Subject's diaries or evaluation checklists
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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, at the medical records facility and within information technology (IT) systems that are involved in the clinical trial

The Investigator/institution will permit clinical trial-related monitoring, audits, IRB/REB/EC review and regulatory inspections by providing direct access to source data/documents related to this clinical trial.

11.1 RECORDS RETENTION

Upon request of the Clinical Monitor, Sponsor or its agent(s), auditor, IRB/REB/EC or regulatory authority, the Investigator/institution should make available for direct access all requested clinical trial-related records.

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

It is the Investigator's responsibility to retain clinical trial essential documents for at least two (2) years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least two (2) years have elapsed since the formal discontinuation of clinical development of the IP. This retention period may be superseded by local requirements. The Sponsor will inform the Investigator/institution when these documents are no longer needed to be retained.

12 SAFETY AND QUALITY MONITORING12.1 SAFETY REVIEW

A safety run-in period will be implemented such that the study will evaluate safety in up to 6 adult subjects prior to opening to full enrollment. This is described in more detail in Section 3.

This trial will not utilize a Data Safety Monitoring Board. This is a single-arm, open-label trial. The Sponsor's Medical Monitor will have access to unblinded safety and tolerability data during the trial. At a minimum, the Sponsor's Medical Monitor will review reported adverse events quarterly.

12.2 CLINICAL MONITORING

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

- Prior to subject screening at the site, a Site Initiation Visit will be conducted to review all relevant forms and documentation, and ensure that the clinical trial site staff are qualified and compliant with all applicable requirements
- All clinical trial site monitoring visits will be documented
- Periodic clinical trial site visits will be performed throughout the clinical trial
- The Clinical Monitor will address and document the following clinical trial conduct activities and obligations:
    - Assure that the clinical trial is being conducted in accordance with the protocol, applicable regulatory authority regulations and IRB/REB/EC policies
    - Discuss clinical trial conduct issues and incidents of noncompliance with the Investigator and/or clinical trial personnel and document them on the Monitoring Visit Report. Report any significant unresolved problems immediately to the Sponsor
    - Remind the Investigator as necessary of the obligation to immediately report all SAEs and DLTs and provide subsequent follow-up report(s) of the final outcome to the IRB/REB/EC
    - Throughout the clinical trial, inspect all source documents to ensure that they are Attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C)
    - Assure that the clinical trial facilities continue to be acceptable
    - Compare the clinical trial CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
    - Assure that investigational drug and study device accountability and reconciliation of records are complete and accurate
    - Assure that all subject specimens are being stored and forwarded properly for testing in accordance with laboratory manual requirements

13 FINANCING AND INSURANCE

Inovio Pharmaceuticals, Inc. is the Sponsor and is funding this study. Clinical trial insurance has been obtained in accordance with the laws of the countries where the study will be conducted. The investigative site is being compensated for the conduct of this study and will follow the terms described in the clinical trial agreement. This agreement was executed separately from this clinical trial protocol. The Investigators will be required to provide full financial disclosure information in accordance with 21CFR Part 54.

14 PUBLICATION POLICY

Publication of the results of this clinical trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to the Sponsor for review and approval in accordance with the governing clinical trial agreement.

15 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original, and Accurate
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
cfHPV DNA	Circulating Free HPV DNA
Cl	Chloride
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMR	Electronic Medical Records
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPC	Glycoprotein
HPV	Human Papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
IM	Intramuscular
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
mITT	modified Intent to Treat
MM	Medical Monitor
mRNA	Messenger RNA
NCS	Not Clinically Significant
NHP	Non-human Primates
pDNA	Plasmid DNA
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PT	Preferred Term
RBC	Red blood cell
RR	Respiratory Rate
RRP	Recurrent Respiratory Papillomatosis
SAE	Serious Adverse Event
sDNA	Synthetic DNA
SID	Subject Identification Number
SMMP	Safety and Medical Monitoring Plan
SOC	System Organ Class
SSC	Saline Sodium Citrate
TEAE	Treatment Emergent Adverse Event

TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

16 REFERENCES

1. Aggarwal C, Cohen RB, Morrow MP, Kraynyak KA, Sylvester AJ, Knoblock DM, et al. **Immunotherapy Targeting HPV16/18 Generates Potent Immune Responses in HPV-Associated Head and Neck Cancer**. *Clin Cancer Res* 2019; 25(1):110-124.
2. Derkay CS, Bluher AE. **Update on Recurrent Respiratory Papillomatosis**. *Otolaryngol Clin North Am* 2019; 52(4):669-679.
3. Major T, Szarka K, Sziklai I, Gergely L, Czeglédy J. **The characteristics of human papillomavirus DNA in head and neck cancers and papillomas**. *J Clin Pathol* 2005; 58(1):51-55.
4. Ivancic R, Iqbal H, deSilva B, Pan Q, Matrka L. **Current and future management of recurrent respiratory papillomatosis**. *Laryngoscope Investig Otolaryngol* 2018; 3(1):22-34.
5. Omland T, Lie KA, Akre H, Sandlie LE, Jebsen P, Sandvik L, et al. **Recurrent respiratory papillomatosis: HPV genotypes and risk of high-grade laryngeal neoplasia**. *PLoS One* 2014; 9(6):e99114.
6. Rosenberg T, Philipsen BB, Mehlum CS, Dyrvig A-K, Wehberg S, Chirilă M, et al. **Therapeutic Use of the Human Papillomavirus Vaccine on Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis**. *The Journal of Infectious Diseases* 2018; 219(7):1016-1025.
7. Lin HW, Richmon JD, Emerick KS, de Venecia RK, Zeitels SM, Faquin WC, et al. **Malignant transformation of a highly aggressive human papillomavirus type 11-associated recurrent respiratory papillomatosis**. *Am J Otolaryngol* 2010; 31(4):291-296.
8. Turner MT, Byrd JK, Ferris RL. **Current Role of Surgery in the Management of Oropharyngeal Cancer**. *J Oncol Pract* 2016; 12(11):1176-1183.
9. Pai SI, Friedman AD, Franco R, Muniappan A, Park JC, Campbell NP, et al. **A phase II study of pembrolizumab for HPV-associated papilloma patients with laryngeal, tracheal, and/or pulmonary involvement**. *Journal of Clinical Oncology* 2019; 37(15_suppl):2502-2502.
10. Shin TH, Pankhong P, Yan J, Khan AS, Sardesai NY, Weiner DB. **Induction of robust cellular immunity against HPV6 and HPV11 in mice by DNA vaccine encoding for E6/E7 antigen**. *Hum Vaccin Immunother* 2012; 8(4):470-478.
11. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC, et al. **Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses**. *SciTranslMed* 2012; 4(155):155ra138.
12. Aggarwal C, Cohen RB, Morrow MP, et al. **Immune Therapy Targeting E6/E7 Oncogenes of Human Papillomavirus Type 6 (HPV-6) Reduces or Eliminates the Need for Surgical Intervention in the Treatment of HPV-6 Associated Recurrent Respiratory Papillomatosis.** *Vaccines* 2020; 8(1):E56
13. Saha R, Killian S, Donofrio RS. **DNA vaccines: a mini review**. *Recent Pat DNA Gene Seq* 2011; 5(2):92-96.
14. Sheets RL, Stein J, Manetz TS, Andrews C, Bailer R, Rathmann J, et al. **Toxicological safety evaluation of DNA plasmid vaccines against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile virus is similar despite differing plasmid backbones or gene-inserts**. *Toxicol Sci* 2006; 91(2):620-630.
15. Sheets RL, Stein J, Manetz TS, Duffy C, Nason M, Andrews C, et al. **Biodistribution of DNA plasmid vaccines against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile virus is similar, without integration, despite differing plasmid backbones or gene inserts**. *Toxicol Sci* 2006; 91(2):610-619.
16. Chattergoon MA, Saulino V, Shames JP, Stein J, Montaner LJ, Weiner DB. **Co-immunization with plasmid IL-12 generates a strong T-cell memory response in mice**. *Vaccine* 2004; 22(13-14):1744-1750.

17. Hanlon L, Argyle D, Bain D, Nicolson L, Dunham S, Golder MC, et al. **Feline leukemia virus DNA vaccine efficacy is enhanced by coadministration with interleukin-12 (IL-12) and IL-18 expression vectors**. *JVirol* 2001; 75(18):8424-8433.
18. Kim JJ, Maguire HC, Jr., Nottingham LK, Morrison LD, Tsai A, Sin JI, et al. **Coadministration of IL-12 or IL-10 expression cassettes drives immune responses toward a Th1 phenotype**. *JInterferon Cytokine Res* 1998; 18(7):537-547.
19. Kim JJ, Trivedi NN, Nottingham LK, Morrison L, Tsai A, Hu Y, et al. **Modulation of amplitude and direction of in vivo immune responses by co-administration of cytokine gene expression cassettes with DNA immunogens**. *EurJImmunol* 1998; 28(3):1089-1103.
20. Operschall E, Schuh T, Heinzerling L, Pavlovic J, Moelling K. **Enhanced protection against viral infection by co-administration of plasmid DNA coding for viral antigen and cytokines in mice**. *JClinVirol* 1999; 13(1-2):17-27.
21. Kalams SA, Parker SD, Elizaga M, Metch B, Edupuganti S, Hural J, et al. **Safety and Comparative Immunogenicity of an HIV-1 DNA Vaccine in Combination with Plasmid Interleukin 12 and Impact of Intramuscular Electroporation for Delivery**. *Journal of Infectious Diseases* 2013.
22. Tebas P, Kraynyak KA, Patel A, Maslow JN, Morrow MP, Sylvester AJ, et al. **Intradermal SynCon® Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers**. *J Infect Dis* 2019.
23. Tebas P, Roberts CC, Muthumani K, Reuschel EL, Kudchodkar SB, Zaidi FI, et al. **Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report**. *N Engl J Med* 2017.
24. Morrow MP, Kraynyak KA, Sylvester AJ, Shen X, Amante D, Sakata L, et al. **Augmentation of cellular and humoral immune responses to HPV16 and HPV18 E6 and E7 antigens by VGX-3100**. *Mol Ther Oncolytics* 2016; 3:16025.
25. Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J, et al. **Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial**. *Lancet* 2015; 386(10008):2078-2088.
26. Morrow MP, Kraynyak KA, Sylvester AJ, Dallas M, Knoblock D, Boyer JD, et al. **Clinical and Immunologic Biomarkers for Histologic Regression of High-Grade Cervical Dysplasia and Clearance of HPV16 and HPV18 after Immunotherapy**. *Clin Cancer Res* 2018; 24(2):276-294.
27. Morrow MP, Tebas P, Yan J, Ramirez L, Slager A, Kraynyak K, et al. **Synthetic Consensus HIV-1 DNA Induces Potent Cellular Immune Responses and Synthesis of Granzyme B, Perforin in HIV Infected Individuals**. *Mol Ther* 2015; 23(3):591-601.
28. Aihara H, Miyazaki J. **Gene transfer into muscle by electroporation in vivo**. *Nat Biotechnol* 1998; 16(9):867-870.
29. Gehl J, Mir LM. **Determination of optimal parameters for in vivo gene transfer by electroporation, using a rapid in vivo test for cell permeabilization**. *Biochem Biophys Res Commun* 1999; 261(2):377-380.
30. Gothelf A, Mir LM, Gehl J. **Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation**. *Cancer Treat Rev* 2003; 29(5):371-387.
31. Cemazar M, Golzio M, Sersa G, Rols MP, Teissie J. **Electrically-assisted nucleic acids delivery to tissues in vivo: where do we stand?** *Curr Pharm Des* 2006; 12(29):3817-3825.
32. Favard C, Dean DS, Rols MP. **Electrotransfer as a non viral method of gene delivery**. *Curr Gene Ther* 2007; 7(1):67-77.

33. Diehl MC, Lee JC, Daniels SE, Tebas P, Khan AS, Giffear M, et al. **Tolerability of intramuscular and intradermal delivery by CELLECTRA(®) adaptive constant current electroporation device in healthy volunteers**. *Hum Vaccin Immunother* 2013; 9(10):2246-2252.
34. Derkay CS, Malis DJ, Zalzal G, Wiatrak BJ, Kashima HK, Coltrera MD. **A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis**. *Laryngoscope* 1998; 108(6):935-937.

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