Official Title:	**A Prospective, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation With CELLECTRA™-5PSP for the Treatment of HPV-16 and/or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Cervix**
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16.1.9 Documentation of Statistical Methods

This section includes the following:

Statistical Analysis Plan version 2.4, dated 02Mar2020

Inovio Pharmaceuticals, Inc.

HPV-301

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITHCELLECTRA™ 5PSP FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE CERVIX

02MAR2020

Statistical Analysis Plan

Version *2.4*

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Adenocarcinoma-in-situ
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIN	Cervical Intraepithelial Neoplasia
CIs	Confidence Intervals
CKC	Cold Knife Conization
Cr	Serum Creatinine
CTCAE	Common Toxicity Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECC	Endocervical Curettage
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EP	Electroporation with CELLECTRA™ 5PSP
HR	High Risk
HPV	Human Papillomavirus
HSIL	High Grade Squamous Intraepithelial Lesion
LEEP	Loop Electrosurgical Excision Procedure
LEETZ	Large Loop Excision of Transformation Zone
IM	Intramuscularly
LR	Low Risk
LSIL	Low Grade Squamous Intraepithelial Lesion
IHC	Immunohistochemistry
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro RNA
mITT	Modified Intent-To-Treat
OR	Odds Ratio
PAC	Pathology Adjudication Committee

PE	Physical Examination
PP	Per Protocol
PRO	Patient Reported Outcomes
PT	Preferred Term
PVG	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
UADE	Unanticipated (Serious) Adverse Device Effects

1. Introduction

Infection with human papillomavirus (HPV) can lead to malignant neoplasia, localized primarily in the anogenital area and aerodigestive tract, in both men and women. HPV types tropic to mucosal tissues are classified into high-risk (HR), based on their potential to cause cancer, and low-risk (LR) (causing generally benign lesions). HPV-16 and HPV-18 are the most significant amongst high-risk types since they are responsible for most HPV-caused cancers [2].

While the currently available prophylactic HPV vaccines (Cervarix™, Gardasil™, and Gardasil™-9) are highly effective in preventing persistent infection and the subsequent development of high-grade Cervical Intraepithelial Neoplasia (CIN) caused by HPV-16, HPV-18 and other HPV types, the prophylactic vaccines have no therapeutic effect upon existing HPV infection or existing HPV-related intraepithelial neoplasia [3]. The current approaches to the management of cervical High grade squamous intraepithelial lesion (HSIL) typically require surgery (i.e. Loop Electrosurgical Excision Procedure/ Large Loop Excision of Transformation Zone (LEEP/LEETZ), laser ablation, or conization); however, surgical excision does not necessarily address the underlying HPV-infection, and can adversely impact the reproductive health of women of childbearing age. Therefore, VGX-3100 is being developed as a non-surgical therapeutic option for the precancerous precursor to cervical cancer, cervical HSIL, and the underlying, pathogenic HPV infection.

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

This statistical analysis plan (SAP) describes the analyses and data presentations for Inovio's protocol "REVEAL 1 Trial". It includes the definitions of analysis populations and derived variables, and describes statistical methods for the analyses of efficacy and safety.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to determine the efficacy of VGX-3100 compared with placebo with respect to combined histopathologic regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18.

2.2. Secondary Objective

The secondary objectives of this study are:

1. Evaluate the safety and tolerability of VGX-3100 delivered intramuscularly (IM) followed by Electroporation (EP) with CELLECTRA™ 5PSP
2. Determine VGX-3100 efficacy compared to placebo as measured by histopathologic regression of cervical HSIL
3. Determine VGX-3100 efficacy compared to placebo as measured by virologic clearance of HPV-16 and/or HPV-18
4. Determine VGX-3100 efficacy compared to placebo as measured by complete histopathologic regression of cervical HSIL to normal
5. Determine VGX-3100 efficacy compared to placebo as measured by both complete histopathologic regression of cervical HSIL to normal and virologic clearance of HPV-16 and/or HPV-18
6. Determine VGX-3100 efficacy compared to placebo as measured by histopathologic non-progression
7. Describe the clearance of HPV-16 and/or HPV-18 infection from non-cervical anatomic locations
8. Determine the humoral and cellular immune response following administration of VGX-3100 compared with placebo at post dose 3 and Week 36 visits as assessed relative to baseline

2.3. Exploratory Objective

The exploratory objectives of this study are:

1. Evaluate tissue immune responses to VGX-3100 in cervical samples
2. Describe association of microRNA (miRNA) profile, DNA methylation profile, previous colposcopy, cytology and HPV testing results with Week 36 histologic regression
3. Describe the durability of virologic clearance of HPV-16 and/or HPV-18 for subjects treated with VGX-3100 compared with those treated with placebo
4. Describe the patient-reported outcomes (PRO) for subjects treated with VGX-3100
5. Determine whether a tissue-based score derived using an immunologic markers (Immunoscore) at baseline is predictive for histological and virological response to VGX-3100 at Week 36

3. Investigational Plan

3.1. Overall Study Design and Plan

HPV-301 is a prospective, randomized, double-blind, placebo controlled, multi-center study to determine the efficacy, safety, and tolerability of VGX-3100 administered by IM injection followed by EP delivered with CELLECTRA™ 5PSP in adult women with histologically confirmed cervical HSIL (CIN2, CIN3) associated with HPV-16/18.

A sample of approximately 198 subjects will be randomized to receive either 6 mg (in 1 ml) VGX-3100 or placebo, each IM followed by EP, in a 2:1 ratio in a stratified manner. To be eligible for the study, subjects age 18 years and above must consent to participate and have cervical biopsy/biopsies of the cervical lesion(s) at the time of screening. Slides of the biopsy will be sent to a Pathology Adjudication Committee (PAC) in a blinded manner to establish the presence of cervical HSIL within screening. In order to be eligible for continued enrollment, the PAC must assign the histologic diagnosis of cervical HSIL. Subjects must also have a cervical specimen test positive for HPV-16 and/or 18 by cobas™ HPV test to be eligible for participation in the study. The Schedule of Events in Appendix 13.1 provides the details of sample collection and assessment.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsy or excisional treatment) and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit.

3.2.2. Secondary Endpoints

The secondary endpoints of this study are:

1. a. Incidence and severity of local and systemic events for 7 and 28 days following each investigational treatment and for the duration of the study (through Week 88 visit)

   b. Incidence and severity of all adverse events including SAEs, SUSAR, UADE and other unexpected AEs for the duration of the study (through Week 88 visit)
2. Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsies or excisional treatment) at Week 36 visit
3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit
4. Proportion of subjects with no evidence of Low grade squamous intraepithelial lesion (LSIL) or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3) on histology (i.e. biopsies or excisional treatment) at Week 36 visit

5. Proportion of subjects with no evidence of LSIL or HSIL (i.e. no evidence of CIN1, CIN2 or CIN3 on biopsies or excisional treatment) on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit
6. Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit
7. Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (oropharynx, vagina and intra-anal) at Week 36 Visit
8. a. Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations at Week 15 and 36 visits

   b. Interferon-γ ELISpot response magnitudes at baseline, Weeks 15 and 36 visits

   c. Flow Cytometry response magnitudes at baseline and Week 15 visits

3.2.3. Exploratory Endpoints

The exploratory endpoints of this study are:

1. Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells. Additional assessments may include visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue as sample allows. Markers listed here may change as new relevant information becomes available
2. Colposcopy, cytology, and HPV test results (Weeks 8, 15 and 28 visits), miRNA profile (baseline, Week 8) and DNA methylation profile (baseline, Week 15) in conjunction with histologic regression of cervical HSIL at Week 36 visit
3. Proportion of subjects with no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Weeks 62 and 88 visits
4. Patient-reported outcome questionnaires self-administered at baseline, after each dose at Weeks 4, 12, 8-14 days following each dose, and at Weeks 28, 36, 40 and 88 by subjects enrolled in US, Canada, Mexico, Germany and UK
5. Immunoscore results for VGX-3100 treated subjects and in conjunction with histological and virological outcomes at Week 36

3.3. Treatments

A total dose of 6 mg VGX-3100 DNA has been selected for this study based on previous human experience with both the WFI/LGS and SSC formulations of VGX-3100, preclinical data with VGX-3100 and other DNA vaccines, and the safety and immunogenicity data generated in the HPV-001, HPV-003, and HPV-101 studies. In HPV-001 trial, the 6 mg dose was delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses compared to the low (0.6 mg) and mid-dose (2 mg) cohorts without significant safety issues [4] . The results

obtained in the phase 2 study suggest that the 6 mg dose was efficacious with an acceptable safety profile, therefore the 6 mg dose will also be evaluated in this Phase 3 trial.

Eligible subjects will receive a 3-dose series of either 6 mg (1 ml) VGX-3100 or Placebo 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 the CELLECTRA™ 5PSP. Study duration is approximately 88 weeks for each subject to finish 3 doses of treatment scheduled at Day 0, Week 4, and Week 12 study visit, and 76 weeks of long-term follow-up.

3.4. Dose Adjustment/Modifications

There is no dose adjustment or modification for this study.

4. General Statistical Considerations

4.1. Sample Size

A total of 198 subjects will be randomized to receive either 6 mg VGX-3100 or placebo IM followed by EP in a 2:1 ratio. This sample size provides 90% power to declare VGX-3100 superior to placebo, assuming the true proportion of subjects who achieve the primary endpoints is 35% and 14% for VGX-3100 and placebo, respectively. These proportions also incorporate missing data (~10%) classified as non-regressors (failures). The assumptions are based on the Phase 2 study results.

4.2. Randomization, Stratification, and Blinding

Subjects will be randomized (2 VGX-3100:1 Placebo) in a stratified manner according to a) the degree of CIN observed in the biopsy specimens at screening (CIN2 vs. CIN3), b) Body Mass Index (BMI) category (≤25 vs. >25 kg/m2) on Day 0 visit, and c) age category (<25 years vs. ≥25 years) on Day 0 visit. There will be no pre-determined number of subjects required to be randomized within each stratum. To ensure that milder CIN2 disease is not over-represented in the study, the percentage of subjects enrolled with CIN2 will not exceed 50% of the total enrolled.

The study is double-blinded to both investigators and subjects.

4.3. Analysis Population

4.3.1. Intent-to-Treat

The intent to treat (ITT) population includes all subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be primary for the analysis of efficacy in this study. Missing data will be considered as non-regressors (failures) for the ITT efficacy analysis. A subject's regression outcome is missing if her CIN grade and HPV clearance at the Week 36 timeframe cannot be determined. Also, any subject who undergoes excision or whose cervix is biopsied at any time

between their initial dose and the Week 36 timeframe will be considered a non-regressor regardless of the Week 36 timeframe result. The ITT population will also be used for summaries of demographics, baseline characteristics, and disposition and protocol deviations.

4.3.2. Modified Intent-to-Treat

The modified intent to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding ITT population for the analysis of efficacy and will also serve as sensitivity analyses regarding missing data.

4.3.3. Per Protocol

The per-protocol (PP) population comprises subjects who receive all doses of Study Treatments and have no protocol violations and who have the analysis endpoint of interest. Subjects in this sample will be grouped to treatment arms as randomized. Analyses on the PP population will be considered supportive of the corresponding ITT population for the analysis of efficacy. Additional analyses on the PP population will utilize the Week 36 timeframe result regardless of any procedure performed before the Week 36 timeframe, thus serving as sensitivity analyses regarding early intervention. Subjects excluded from the PP population will be identified and documented prior to unblinding of the study database.

4.3.4. Safety

The safety analysis population includes all subjects who receive at least one dose of Study Treatment. Subjects will be analyzed as to the treatment they actually received.

4.4. Report Conventions

The following reporting conventions apply generally to tables, listings, and figures:

- Data from all study centers will be combined for analysis;
- P-values will be rounded to 3 decimal places. P-values that round to 0.000 will be presented as ‘<0.001’ and p-values that round to 1.000 will be presented as ‘>0.999’;
- Confidence intervals (Cis) will be presented as 2-sided 95% Cis unless specified differently for a given analysis;
- Summary statistics will consist of the number and percentage of subjects in each category for categorical variables, and the sample size, mean, standard deviation (SD), median, minimum, and maximum for continuous variables;
- Unless otherwise specified, all mean and median values will be formatted to 1 more decimal place than the measured value, standard deviation values will be formatted to 2 more decimal places than the measured value, and minimum and maximum will be formatted to the same decimal place as the measured value;

- All percentages will be rounded to 1 decimal place. The number and percentage of responses will be presented in the form XX (XX.X);
- Unless otherwise specified, all analyses and summary tables will have the analysis population sample size (i.e., number of subjects), and displayed by the treatment arm and total;
- Subjects who received mixed treatments will not be included in the summaries of overall safety according to the assigned treatment arm; their data will be reported elsewhere.
- All collected data will be listed.
- SAS® Version 9.3 or higher will be the statistical software package used to produce all data summaries, listings, and statistical analyses.

4.5. Baseline Definition

Baseline is defined as the last measurement prior to the first treatment administration. If the first treatment date is not available, the last measurement before or on the randomization date will be used.

4.6. Study Day

The day of the first study treatment is defined as Day 1. Study day for a particular event date is calculated as (Date of event – Date of Day 1 + 1) if the event occurs on or after Day 1, or (Date of event – Date of Day 1) if the event occurs prior to Day 1, and the study day of any event prior to the first study treatment will be a negative number. Duration of an event will be calculated as (Event end date – Event start date +1).

5. Subject Disposition

5.1. Disposition

Number and percentage of subjects in each analysis population will be summarized by treatment arm and total.

Additionally, the number and percentage of subjects who received each dose, complete all electroporation/study treatments, completed all study visits, discontinued study treatment, and early withdraw from the study will be presented. The reasons for study treatment discontinuation and early withdrawal from study will also be summarized.

A disposition of subjects by country and site, and by treatment will also be summarized.

5.2. Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be identified in cooperation with the sponsor. All subjects excluded from the PP population will also be identified. These identifications will be defined prior to database lock.

The number and percentage of subjects with protocol deviations will be summarized. Subjects excluded from the PP population will be presented separately.

6. Demographics and Baseline Characteristics

6.1. Demographics

Age (years), height (cm), weight (kg), BMI (kg/m^2), and years of education (years) will be summarized as continuous variables. BMI (in kg/ m^2) is defined as the subject's weight (in kg) divided by the square of their height (in m). The number and percentage of subjects will be presented for categorical variables including race, ethnicity, gender, stratification factors (CIN grade (CIN2 vs. CIN3), BMI (≤25 vs. >25), age (<25 vs. ≥25)), and type(s) of healthcare insurance.

A separate listing will be provided for stratification errors.

6.2. Reproductive History and Status

The number and percentage of subjects with reproductive potential and current use of contraception method will be summarized. For the subjects who are not of reproductive potential, the reason will be summarized.

For the subjects who have ever been pregnant, the age of first pregnancy, as well as pregnancy related information will be summarized based on the collection at screening.

6.3. Alcohol and Tobacco Usage

The number of subjects who consumed alcohol, number of alcoholic drinks per day, and number of drink days per week will be summarized.

Passive smoking will be summarized by number of subjects with history of exposure, living with a permanent householder who smokes daily, and number of hours/day of passive smoke.

Smoking will be summarized by the smoke type and duration of smoke. For the cigarette type, number of packs/day will also be summarized. Duration of smoke is calculated by (the stop year-start year+1) when both years are available. If the stop year is ongoing, it will be set to the year of the study visit.

Substance usage will be summarized at Screening, Week 36, and Week 88. Number of subjects with change from baseline will also be summarized at each post-baseline visit

6.4. Medical History

6.4.1. General Medical History

Data for general medical history will be presented in a listing.

6.4.2. Disease-Specific History

The number and percentage of subjects exposed to prophylactic HPV vaccine will be summarized. For the subjects who had a prior CIN diagnosis the following will be summarized: CIN grade, received prior treatment (Y/N), and time from initial diagnosis. For the subjects who had prior treatment, the type of last treatment and time from the last treatment will be summarized. Time from the most recent Pap smear prior to screening and results will also be summarized.

Time from initial diagnosis = date of randomization- date of initial diagnosis.

Time from the last treatment = date of randomization- date of the last treatment .

Time from the most recent Pap smear = date of randomization- date of the most recent pap smear .

These calculations will be done only when the dates are available, and no imputation is applied for these missing dates.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

For the purpose of inclusion in prior and/or concomitant medication summaries, incomplete medication stop dates will be imputed; start dates will not be imputed.

Missing stop dates will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: impute to the last day of the month;
- DD-UNK-YYYY: impute to DD-DEC-YYYY;
- DD-MMM-UNKN: impute to DD-MMM-YOLV, where YOLV is year of subject's last study visit;
- UK-UKN-YYYY: impute to 31-DEC-YYYY;
- UK-MMM-UNKN: impute to LD-MMM-YOLV, where LD is the last day of MMM and YOLV is year of subject's last study visit;
- DD-UNK-UNKN: impute to DD-DEC-YOLV, where YOLV is year of subject's last study visit;
- UK-UKN- UNKN: impute to day of subject's last study visit.

If the imputed stop date is before the raw start date, then the imputed stop date will be set as the same as the start date.

All medications will be coded according to the latest version of World Health Organization drug dictionary.

The mITT population will be used for the main summaries of medication. If there are subjects who are included in ITT population but not the mITT population for medications, which will consist of those who are randomized but never dosed, then their medication data will be summarized separately and always considered to be prior medication by definition.

7.1.1. Prior Medications

A prior medication is defined as any medication that has a stop date before the first dose of study drug (prior to Day 1). The number and percentage of subjects with at least one prior medication will be summarized by treatment arm. The number and percentage of subjects with each prior medication will be summarized by treatment arm and by drug class and preferred term.

7.1.2. Concomitant Medications

A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study drug. The number and percentage of subjects with at least one concomitant medication will be summarized by treatment arm. The number and percentage of subjects with each concomitant medication will be summarized by treatment arm and by drug class and preferred term.

7.2. Study Treatments

Number of doses taken and percentage of subjects at number of doses will be summarized by the treatment arm.

8. Efficacy Analysis

All of the efficacy endpoints analyses will use the ITT population. Analyses of primary and secondary efficacy endpoints with the mITT and PP populations will be considered supportive of the corresponding ITT population.

Subgroup analysis of the primary and secondary efficacy endpoints will also be conducted by history of exposure to prophylactic HPV vaccines.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with no evidence of cervical HSIL (i.e. no evidence of CIN2, CIN3) on histology (i.e. biopsies or excisional treatment)

and no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at the Week 36 timeframe.

The primary hypothesis of superiority is:

H0: $\delta \leq 0$ vs. H1: $\delta > 0$,

where $\delta = Pv - Pp$, and Pv and Pp denote the true population probabilities of the primary endpoint for VGX-3100 and Placebo, respectively. The proportion in each treatment arm is calculated by the number of responders divided by the total number of responders and non-responders in the study population of the corresponding treatment arm. The detailed definitions of responder and non-responder are listed in Table 1.

For the primary endpoint, week 36 histology is evaluated based on the first biopsy or surgical excision procedure on or after Day 238; in case of multiple results on the same day, the one with worst grade will be used. The virology results used for analysis must be the latest result that is on or before the same date as the histology result and is taken on or after Day 238. If a subject undergoes excision or cervical biopsy at any time on or after Day 1 and before Day 238, the subject will be considered as non-responder.

Number of responders and non-responders, proportion of responders in each treatment arm, and difference of proportions between the two treatment arms will be presented. A p-value of superiority based on a test of risk difference and corresponding 95% confidence interval using the method of Miettinen and Nurminen [5] will be computed. Superiority will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the 95% CI exceeds zero.

Responder proportion will also be summarized based on the stratification factors separately.

Table 1. Definition of Primary Endpoint Responder and Non-Responder

Responder	**Non-Responder**
Subject with no histologic evidence of cervical HSIL[a] at Week 36 evaluation and no evidence of HPV-16 and/or HPV-18 at Week 36[b] AND Subject in which an excision or biopsy sample[c] was NOT obtained between initial dose up to Week 36	Subject with histologic evidence of cervical HSIL, Adenocarcinoma-in-situ (AIS), cervical carcinoma at Week 36 OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result

a. No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL

b. The histopathologic efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36. The first tissue removal sample in this time frame determines the histology endpoint. The most recent HPV clearance result prior to tissue removal, which includes results from the same date, within the time frame determines the HPV clearance endpoint.

c. Excludes ECC-only samples

8.2. Secondary Efficacy Endpoints

For the secondary efficacy endpoints listed in Section 3.2.2 of this SAP, the analysis method will be the same as for the primary endpoint described in Section 8.1, but without p-values.

In addition, the definition of responder and non-responder for each endpoint is defined in Table 2.

Table 2. Definition of Secondary Endpoints Responder and Non-Responder

Endpoint	Responder	Non-Responder
Proportion of subjects with no evidence of cervical HSIL on histology (i.e. biopsies or excisional treatment) at Week 36 visit	Subject with no histologic evidence of cervical HSIL[a] at Week 36[b] AND Subject in which an excision or biopsy sample[c] was NOT obtained between initial dose up to Week 36	Subject with histologic evidence of cervical HSIL, AIS, cervical carcinoma at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result
Proportion of subjects with no evidence of HPV-16 and/or HPV-18 in cervical samples by type specific HPV testing at Week 36 visit	Subject with no evidence of HPV-16 and/or HPV-18[d] at Week 36 AND Subject in which an excision or biopsy sample was NOT obtained between initial dose up to Week 36	Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result
Proportion of subjects with no evidence of squamous atypia, LSIL, or HSIL on histology (i.e. biopsies or excisional treatment) at Week 36 visit	Subject with no histologic evidence of cervical HSIL, squamous atypia, or LSIL[e] at Week 36 AND Subject in which an excision or biopsy sample was NOT obtained between initial dose up to Week 36	Subject with histologic evidence of cervical HSIL, squamous atypia, LSIL, AIS, cervical carcinoma at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result

Proportion of subjects with no evidence of squamous atypia, LSIL or HSIL on histology (i.e. biopsies or excisional treatment) and no evidence of HPV-16 and/or HPV-18 by type specific HPV testing at Week 36 visit	Subject with no histologic evidence of cervical HSIL squamous atypia, or LSIL at Week 36 and no evidence of HPV-16 and/or HPV-18 at Week 36 AND Subject in which an excision or biopsy sample was NOT obtained between initial dose up to Week 36	Subject with histologic evidence of cervical HSIL, squamous atypia, or LSIL AIS, cervical carcinoma at Week 36 OR Subject with evidence of HPV-16 or HPV-18 at Week 36 OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result
Proportion of subjects with no progression of cervical HSIL to cervical carcinoma from baseline on histology (i.e. biopsies or excisional treatment) at Week 36 visit	Subject with no histologic evidence of a worsening cervical condition at Week 36 relative to baseline AND Subject in which an excision or biopsy sample was NOT obtained between initial dose up to Week 36	Subject with histologic evidence of worsening of cervical condition at Week 36 relative to baseline OR Subject in which an excision or biopsy sample was obtained between initial dose up to Week 36 OR Subjects with no Week 36 sample result
Proportion of subjects who have cleared HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations (i.e., oropharynx, vagina and intra-anal) at Week 36 visit	Subject with no evidence of HPV-16 and/or HPV-18 on specimens from non-cervical anatomic locations[f] at Week 36	Subject with evidence of HPV-16 or HPV-18 on specimens from non-cervical anatomic locations at Week 36 OR Subjects with no Week 36 sample result

a. No evidence of HSIL is defined by histology as negative, squamous atypia, or LSIL. The first tissue removal sample within the timeframe determines the histology endpoint.

b.The efficacy time frame is defined by those who have undergone a biopsy or surgical excision at any time starting from 14 days prior to the protocol-specified target date of Week 36

c. Excludes ECC-only samples

d.The most recent HPV clearance result prior to first tissue removal, which includes results from the same date, within the time frame determines the HPV clearance endpoint.

e. No evidence of squamous atypia, CIN1, CIN2 or CIN3 on biopsies or excisional treatment

f. Based on HPV-16 and/or HPV-18 positive specimen at baseline. Subjects will be classified according to the presence/absence of HPV-16 and/or HPV-18 at baseline by each of the three anatomic locations.

8.3. Immunogenicity Analyses

Levels of serum anti-HPV-16 and anti-HPV-18 antibody concentrations and Interferon-γ ELISpot response magnitudes will be assessed from sera and PBMCs isolated from whole blood, respectively, collected at baseline, Week 15, and Week 36 visits. Flow Cytometry response magnitudes will be assessed from PBMCs isolated from whole blood collected at baseline and Week 15 visits.

All of the endpoints will be summarized as continuous variables at each visit. Increases from baseline for each post baseline visit from ELISpot and Flow Cytometry, and titers for each post baseline visit from ELISA will be compared between treatment arms. These comparisons will be analyzed with difference in medians and associated exact non-parametric 95% CIs.

The mITT population with at least one immunogenicity measurement will be used for these immunogenicity analyses.

8.4. Exploratory Analysis

The relationship between the histologic regression of cervical HSIL with virologic clearance at Week 36 visit (Y/N) and a) miRNA results, b) DNA methylation results, c) colposcopy results, d) cytology results, e) HPV results, and f) baseline immunoscore results (tissue-based score derived using immunologic markers) will be examined using separate logistic regression models for each result, with histologic regression of cervical HSIL with virologic clearance as the response variable, and each of the results and treatment arm as regressor variables. Odds Ratios (ORs) and corresponding 95% CIs will be provided for the regressor variables.

Durability, as measured by clearance of HPV-16 and/or HPV-18 infection at Week 62 and 88, will be summarized by number and percentage of subjects with no evidence of HPV-16 and/or HPV-18 by treatment arm at each visit. Specifically, the virology results at Week 62 are those between Day 420 and Day 448, and the virology results at Week 88 are those between Day 602 and Day 630.

Assessment of markers including but not limited to CD8+ and FoxP3+ infiltrating cells, and visualization of Granulysin, Perforin, CD137, CD103 and PD-L1 in cervical tissue may be performed. Markers listed here may change as new relevant information becomes available. These tissue response magnitudes will be compared between treatment arms using a difference in means and associated t-distribution based 95% CIs for changes from baseline at each post-baseline time point.

<u>Patient-Reported Outcomes</u>

Subjects enrolled in US, Canada, Mexico, Germany and UK will complete Patient-reported outcome (PRO) questionnaires (SF-36, EQ-5D-5L, and two additional Global PRO questions assessing quality of life after excision or biopsy). Either SF-36 or EQ-5D-5L or both instruments will be completed at baseline, Weeks 4, and Week 12, 8-14 days following each dose, 8 -14 days post Week 28, Week 36, 8-14 days post Week 40 and

Week 88. The two additional Global PRO questions assessing quality of life after excision or biopsy will be completed at Week 40.

For the SF-36, section scores at each of the eight domains (Physical functioning, Role limitations due to physical problems, Bodily pain, General health, Vitality, Social functioning, Role limitations due to emotional problems, and Mental health) and score change from baseline will be summarized at each visit by treatment arm. Scoring of the eight SF-36 subscales will be done by QualityMetric Health Outcomes(tm) Scoring Software 5.0.

For the EQ-5D-5L, each of the five domains (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression) and Global Health Status Score will be summarized at each visit and relative to baseline by treatment arm.

For the two additional Global PRO questions assessing quality of life after excision or biopsy, the time outcome and the binary outcomes to Y/N question will be summarized by treatment arm.

SF-36 scores will be compared between treatment arms using exact non-parametric 95% confidence intervals for the differences in median changes from baseline. The EQ-5D-5L scores will be analyzed in the same fashion. Days of worsened quality of life for the Week 40 Quality of Life questionnaire will be analyzed using an exact non-parametric 95% confidence interval for the difference in the median number of days. The Y/N worsened quality of life response for the Week 40 Quality of Life questionnaire will be analyzed using a 95% Miettinen and Nurminen confidence interval for the difference in proportions between treatment arms.

In addition, PRO endpoints at each visit that occurs after Week 36 will be summarized according to those with excision (excluding biopsy) versus those without.

The mITT population with at least one post baseline corresponding measurement will be used for PRO analyses.

9. Safety Analysis

All safety summaries and analyses will be based on all subjects in the safety analysis set.

9.1. Adverse Events

A pretreatment event is defined as any event that occurs prior to administration of any study treatment; it does not necessarily have to have a causal relationship with study participation. A treatment emergent adverse event (TEAE) is defined as any event temporally associated with the use of a product whether or not considered related to the use of the product. Adverse event (AE) verbatim reported terms will be coded by SOC and PT using the latest version of MedDRA.

For the purpose of inclusion in AE summaries/analyses, incomplete start and stop dates will be imputed as follows:

Missing start dates will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: if MMM and YYYY are the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to 01-MMM-YYYY;
- DD-UNK-YYYY; if DD and YYYY are the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to DD-JAN-YYYY;
- DD-MMM-UNKN; if DD and MMM are the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to DD-MMM-YOSCR, where YOSCR is year subject was initially screened;
- UK-UKN-YYYY: if YYYY is the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to impute to 01-JAN-YYYY;
- UK-MMM-UNKN: if MMM is the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to 01-MMM-YOSCR, where YOSCR is year subject was initially screened;
- DD-UNK-UNKN: if DD is the same as that of 1st dose, then impute to same date as 1st dose; otherwise impute to impute to DD-JAN-YOSCR, where YOSCR is year subject was initially screened;
- UK-UKN- UNKN: impute to date of subject's 1st dose.

If the imputed start date is after the raw stop date, then the imputed start date will be set as the same as the stop date.

Missing stop dates will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: impute to the last day of the month;
- DD-UNK-YYYY: impute to DD-DEC-YYYY;
- DD-MMM-UNKN: impute to DD-MMM-YOLV, where YOLV is year of subject's last study visit;
- UK-UKN-YYYY: impute to 31-DEC-YYYY;
- UK-MMM-UNKN: impute to LD-MMM-YOLV, where LD is the last day of MMM and YOLV is year of subject's last study visit;
- DD-UNK-UNKN: impute to DD-DEC-YOLV, where YOLV is year of subject's last study visit;
- UK-UKN- UNKN: impute to day of subject's last study visit.

If the imputed stop date is before the raw or imputed start date, then the imputed stop date will be set as the same as the start date.

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

AE summary tables will include numbers and percentages of subjects experiencing at least one event by treatment arm. The following is a list of AE summary tables to be generated:

- Overview of AE, AE with onset within 28 days/7 days after study treatment
- TEAEs, TEAEs with onset within 28 days/7 days after study treatment by SOC and PT
- TEAEs, TEAEs with onset within 28 days/7 days after study treatment by Dose Number, SOC and PT
- TEAEs, TEAEs with onset within 28 days/7 days after study treatment by Dose Number, CTCAE Grade, SOC and PT
- Serious TEAEs by Dose Number, SOC and PT
- TEAEs, TEAEs with onset within 28 days/7 days after study treatment by Dose Number, Relationship to IP and EP, SOC and PT
- Serious TEAEs, serious TEAEs with onset within 28 days/7 days after study treatment by Dose Number, Relationship to IP and EP, SOC and PT
- Grade >=3 TEAEs, Grade >=3 TEAEs with onset within 28 days/7 days after study treatment by Dose Number, SOC and PT
- Grade >=3 TEAEs, Grade >=3 TEAEs with onset within 28 days/7 days after study treatment by Dose Number, Relationship to IP and EP, SOC and PT
- TEAEs with Action of Study Treatment Held, TEAEs with Action of Study Treatment Held with onset within 28 days/7 days after study treatment by Dose Number, SOC and PT
- TEAEs with Action of Study Treatment Permanently Discontinued, TEAEs with Action of Study Treatment Permanently Discontinued with onset within 28 days/7 days after study treatment by Dose Number, SOC and PT

Additional AE/SAE summary tables may be added as appropriate.

A subject with 2 or more different adverse events within the same level of the MedDRA term and regimen will be counted only once in that level using the most extreme incident (most severe for the intensity analyses, and related for the relationship to study drug analyses). For the AE with missing relationship to drug/procedure will be imputed as related. TEAEs by dose will be counted by the AE onset date not earlier than the date of treatment and earlier than the subsequent treatment for the first dose and second dose, and any AEs with onset date on or later than the third dose will all be counted to the third dose.

Data listings will be provided for AE, SAE, TEAE leading to treatment discontinuation, TEAE with CTCAE Grade >=3, TEAE with onset within 28 days/7 days after study treatment, and AEs resulting in death separately.

9.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) are the adverse events deemed related to VGX-3100/placebo delivered with CELLECTRA™ 5PSP that require expedited communication from the Site to the Sponsor and meet any of the following criteria:

- Grade 3 or greater persistent administration site erythema, and/or induration recorded ≥ 2 hours immediately after Study Treatment
- Grade 4 or greater persistent administration site pain, tenderness recorded ≥ 2 hours immediately after Study Treatment
- Grade 3 or greater fever
- Grade 3 or greater systemic symptoms, including generalized pruritus

An AE summary table will include numbers and percentages of subjects experiencing at least one AESI by dose number, SOC and PT.

9.1.2. Incidence of Adverse Events

For the adverse events with onset date within 28 days after any dose, the frequency of SOC and PT events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen [5] . As this analysis will use many event categories and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals.

A similar analysis will be provided for adverse events within 7 days after any dose and for adverse events during the study after any dose.

9.2. Clinical Laboratory Evaluations

Laboratory evaluations (including hematology, serum chemistry, and urinalysis) will be collected at the screening visit (within 30 days prior to Day 1), and a summary of screening information will be provided by treatment arm and by total.

9.3. Vital Sign Measurements

Vital sign data will be summarized at each visit by treatment arm. Changes from baseline to each scheduled post-baseline visit will be presented as well.

9.4. Physical Examination

During physical examinations, body systems will be assessed as normal, abnormal, or not examined at each scheduled visit, and the percentage of subjects with abnormal physical examination findings at each time point will be summarized by body system and by treatment arm.

9.5. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at Screening after the subject has been in a supine position for 10 to 15 minutes. ECG results will be summarized by treatment arm and by total, for interpretation results including Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Not Done.

10. Interim Analysis

For reasons of futility (early evidence of poor efficacy of VGX-3100) or safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The type I error of 0.05 will not be adjusted for possible early stopping due to futility.

Group-level unblinded (VGX-3100, Placebo) summaries and analyses of efficacy will be produced once the primary endpoint Week 36 visit data are completed for all subjects; subject-level blinding will be maintained. Long-term follow-up data will continue to be collected for all subjects with remaining visits through the final Week 88 visit. The summaries and analyses will allow the Sponsor to have results with respect to the primary endpoint and all other efficacy endpoints corresponding to the cervix and the Week 36 visit on which to make decisions regarding the VGX-3100 program, while still gathering secondary and exploratory endpoint and safety data through the final Week 88 visit. The planned set of summaries and analyses is comprised of a) the primary composite endpoint of histopathologic regression and virologic clearance, b) the secondary endpoint of histopathologic regression, c) the secondary endpoint of virologic clearance, d) the secondary composite endpoint of histopathologic regression to normal and virologic clearance, e) the secondary endpoint of histopathologic regression to normal, and f) the secondary endpoint of histopathologic non-progression. None of these summaries or analyses will be provided if the total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group relative to this total count is less than 3% for a given summary/analysis. Also, items a) through f) are planned to be produced in the order in which they are listed, but as there are intersecting endpoints among these items, items among b) through f) will not be produced if the difference in total count of subjects who experience the event of interest is greater than 0 and the count for any treatment group is 0, relative to any preceding item in the set. The group-level unblinded (VGX-3100, Placebo) production of the summaries and analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), PPD, which has already been providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded with respect to subject treatment assignment throughout the trial. The type I error of 0.05 will not be adjusted for this procedure.

11. Changes in the Planned Analysis

The following changes from the protocol have been made in the planned analysis:

- In section 4.3.3, additional analyses on the PP population are added to serve as sensitivity analyses regarding early intervention. These are not specified in protocol.
- In Table 2, for the clearance from non-cervical anatomic locations endpoint, the table states that excision or biopsies performed on or after Day 1 but before the Week 36 timeframe will not be used to define responder/non-responder, as these procedures should not impact the Week 36 timeframe results for this endpoint. This was not specified in Table 11 of the protocol.

12. References

1. A Prospective, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of VGX-3100 Delivered Intramuscularly Followed by Electroporation with Cellectra™ 5PSP for the Treatment of HPV-16 And/Or HPV-18 Related High Grade Squamous Intraepithelial Lesion (HSIL) of the Cervix, Version 3.0, 23 September 2016.
2. Centers for Disease C, Prevention. Human papillomavirus-associated cancers - United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2012,61:258-261.
3. Future II Study Group. Supplementary Material: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007,356:1915-1927.
4. Bagarazzi ML, Yan J, Morrow MP, Shen X, Parker RL, Lee JC, et al. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Sci.Transl.Med. 2012,4:155ra138.
5. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985,4:213-226.

13. Appendices

13.1. Schedule of Events

Tests	Screening (-10 weeks to -1 Day from Date of Biopsy)	Weeks												
		Day 0	8-14 days post Day 0 Phone Call	4 (± 4 days)	8-14 days post Week 4 Phone Call	8 (± 4 days)	12 (± 4 days)	8-14 days post Week 12	15 (± 1 week)	28 (± 1 week)	36 (± 1 week)	40 (± 2 weeks) Phone call	62 (± 2 weeks)	88 (± 2 weeks)
Informed consent	X													
Medical History	X													
Demographics	X													
Socio-behavioral[a]	X										X			X
Inclusion / Exclusion	X	X												
Randomization		X												
Physical exam/assessment[b]	X	X		X		X	X		X	X	X		X	X
Vital signs	X[c]	X		X		X	X		X	X	X		X	X
Screening safety[d]	X													
Pregnancy Test[e]	X	X		X			X		X	X	X		X	X
HIV Antibody Testing	X													
Blood immunologic samples[f]	X	X				X			X[g]		X			
Cervical Digene swabs[i,j]	X	X							X	X	X			
ThinPrep™ [h,i]	X	X				X			X	X	X		X	X
Colposcopy, lesion photograph[k]	X[l]	X							X	X	X		X	X
Ectocervical biopsy[m]	X										X[n]			
Surgical excision[m]											X[n]			
OP rinse, vaginal swabs		X									X			X
Intra-anal swabs[o]		X									X			
Inject VGX-3100/Placebo		X		X			X							
Post treatment assessment		X	X	X	X	X	X	X[q]	X					
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Distribute PDC		X		X			X							
Review PDC			X		X	X		X[q]						
PROs[p]		X	X	X	X		X	X[q]		X	X	X		X

a Socio-Behavioral assessments, e.g. self-reported smoking and alcohol history

b Full physical examination (PE) mandatory at screening and study discharge (Week 88), otherwise targeted physical assessment as determined by the Investigator or per subject complaints unless signs or symptoms dictate the need for a full PE;

c Screening vital signs must include a measured height and weight. Weight will be collected on Day 0, Weeks 4 and 12;

d Screening safety includes 12-Lead ECG, complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine (Cr), serum glucose, serum ALT, serum CPK and urinalysis performed within 45 days prior to Day 0;

e For WOCBP, a negative spot urine pregnancy test is required at screening and prior to each study treatment, colposcopy and surgical excision;

f At least 34 mL [4 x 8.5 mL yellow (ACD) tubes] whole blood per time point and 8 mL serum per time point at Screening, Day 0 and Week 8 (4 ml serum per time point at Week 15 and 36). A total of at least 68 mL of whole blood and 16 ml serum should be collected prior to dosing on Day 0.

g At least 51 mL [6 x 8.5 mL yellow (ACD) tubes] whole blood and 4 mL serum should be collected at Week 15;

h HPV genotyping and Pap smears are performed on the same ThinPrep™ cervical specimen;

i Request that the subject abstain from sexual activity and refrain from use of douching or vaginal lubricants/medication for a period of 24 hours prior to cervical specimen collection;

j Collected prior to the ThinPrep™ sample;

k A photograph of the lesion with at least one attempt should done as follows: Acetic acid should first be applied to the cervix then photographs of the cervix and the associated lesion should be photographed prior to and after biopsies (if applicable) and at all colposcopic examinations; if repeat photographs are sought, they should be done at the next protocol-specified colposcopy visit.

l Screening colposcopy is optional if adequate colposcopy was performed upon collection of initial biopsy;

m Screening biopsy of the lesion should be collected as Paraffin-embedded cervical tissue, fresh cervical tissue, or H&E slides. Tissue to be analyzed for evidence of histopathologic regression will be obtained at Week 36 visit either by excision (e.g. LEEP, LLETZ, CKC) or by 4 Quadrant Biopsy or 4 Quadrant Biopsy with ECC based upon the assessment at Week 28 of cytology, HR HPV status, and colposcopic findings (See Tables 4 and 5);

n Slides from biopsy and/or excised tissue must be reviewed by the PAC and residual cervical tissue from screening and/or Week 36 specimen(s) (paraffin blocks or unstained slides) may be used for immunohistochemistry (IHC) and HPV testing;

o To be collected only if subject consents for intra-anal sample collection

p One or both PRO questionnaires (i.e. SF-36 and EQ-5D-5L) will be completed by subjects enrolled in USA, Canada, Mexico, Germany and UK at multiple visits during the study. Additional quality of life questions will be asked at the Week 40 phone call. Refer to Section 6.8 for details

q Activities at 8 to 14 days Post-Dose 3 phone call may be done at Week 15 if timing overlaps.

PPD	PPD Biostatistics and Programming
	Statistical Analysis Plan (SAP) Client Approval Form

Client:	Inovio
Protocol Number:	Inovio HPV-301

Document Description:	Final Statistical Analysis Plan
SAP Title:	A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF VGX-3100 DELIVERED INTRAMUSCULARLY FOLLOWED BY ELECTROPORATION WITHCELLECTRA™ 5PSP FOR THE TREATMENT OF HPV-16 AND/OR HPV-18 RELATED HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) OF THE CERVIX
SAP Version Number:	Version 2.4
Effective Date:	02MARCH2020

Author(s):

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I approve this document
02 Mar 2020 12:05:46 -05:00

Approved by:

[redacted]

[redacted]
Date *(DD-MMM-YYYY)*

Inovio Pharmaceuticals, Inc.