Official Title:	**Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine Against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure**
NCT Number:	NCT04642638
Document Dates:	Protocol Version 7.0: 08 March 2022 Protocol Version 6.0: 30 April 2021 Protocol Version 5.0: 02 April 2021 Protocol Version 4.0: 13 November 2020 Protocol Version 3.0: 19 August 2020 Protocol Version 2.0: 15 June 2020 Protocol Version 2.0 (US): 08 October 2021 Protocol Version 1.0: 22 May 2020 Protocol Version 1.0 (US): 30 July 2021

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Original Protocol Version 1.0, dated 22 May 2020

Protocol Version 2.0, dated 15 Jun 2020

Protocol Version 3.0, dated 18 Aug 2020

Protocol Version 4.0, dated 13 Nov 2020

Protocol Version 5.0, dated 02 Apr 2021

Protocol Version 6.0, dated 30 Apr 2021

Protocol Version 7.0, dated 08 Mar 2022

The Sponsor terminated the study while the clinical trial operated under Protocol Version 6.0. Protocol Version 7.0 was not implemented into the study.

Regional Protocols

Protocol Version 1.0 (US), dated 30 Jul 2021

Protocol Version 2.0 (US), dated 08 Oct 2021

COVID19-311

Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Adults at High Risk of SARS-CoV-2 Exposure

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 1.0

Protocol Version Date: 22-May-2020

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically Signed]

[redacted] M.D., Ph.D. Date (ddMmmyyyy)
[redacted]
Inovio Pharmaceuticals, Inc.

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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: _____

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 3

Estimated Number of Clinical Trial Centers and Countries/Regions: Up to 30 centers in the US

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 disease in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is a Phase 3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800 (1.0mg), administered by intradermal (ID) injection followed immediately by electroporation (EP) using CELLECTRA® 2000 device using a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objective of this trial is to evaluate the efficacy of INO-4800 in seronegative subjects.

Approximately 3438 seronegative subjects and 100 seropositive subjects 18 years of age or older are expected to be enrolled and will be randomized at a 1:1 ratio to receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001). See Table 1.

Table 1: COVID19-311 Dose Groups

Study Group	Expected Number of Seronegative Subjects	Number of Seropositive Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	Total Dose
INO-4800	1719	50	0, 28	1	1.0 mg	2.0 mg
Placebo	1719	50	0, 28	1	0	0
Total	3438	100				
Grand Total	3538					

The trial is case-driven. Among seronegative subjects, a total of 89 observed cases will be required for 90% power to declare the vaccine efficacious (>15%), assuming a true efficacy of 60%. A sample size of 3438 seronegative subjects is expected to be required to achieve this number of cases assuming an underlying attack rate of 3.7%. The sample size may be increased if the underlying attack rate is lower than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 6-months post-dose 2. Subjects will be followed for 12 months post-dose 2.

All subjects, investigating site staff (excluding site pharmacy staff) and the Sponsor will be blinded throughout the trial. A group-level unblinding will occur when all subjects' data is complete for the primary efficacy timeframe.

A Data Safety Monitoring Board (DSMB) will convene regularly throughout the trial to review unblinded safety data and adjudicate the cases of COVID-19 disease. Details of its scope will be provided in a charter.

Criteria for Evaluation:

Research Hypothesis:
INO-4800 delivered ID followed by EP using CELLECTRA® 2000 will provide protection against laboratory-confirmed COVID-19 in subjects at high risk of SARS-CoV-2 exposure.

Primary Objective	Associated Primary Endpoints
1. Evaluate the efficacy of INO-4800 in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of laboratory-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline
Secondary Objectives	**Associated Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of injection site reactions 1b. Incidence of systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of injection site reactions, systemic AEs by SOC, PT, severity and relationship to investigational product, SAEs, and AESIs in subjects who are SARS-CoV-2 seropositive at baseline
2. Evaluate the efficacy of INO-4800 of laboratory-confirmed severe or critical COVID-19 cases for 6 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of severe or critical COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 2b. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects requiring mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 2c. Incidence of deaths due to COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2
3. Evaluate the efficacy of INO-4800 with respect to SARS-CoV-2 infections who are SARS-CoV-2 seronegative at baseline	3. Incidence of laboratory-confirmed SARS-CoV-2 infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2

4. Evaluate efficacy of INO-4800 for 12 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline	4a. Incidence of laboratory-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until End of Study (EOS) in subjects who are SARS-CoV-2 seronegative at baseline 4b. Incidence of severe or critical COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 4c. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects requiring mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery starting 14 days after completion of the 2-dose regimen until EOS 4d. Incidence of deaths due to COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 4e. Incidence of laboratory-confirmed SARS-CoV-2 infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
5. Evaluate the short-term efficacy of INO-4800 following one dose in subjects who are SARS-CoV-2 seronegative at baseline	5. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days post-dose 1 until 14 days post-dose 2
6. Evaluate the timing of symptom resolution in subjects who develop COVID-19 illness who are SARS-CoV-2 seronegative at baseline	6. Days to symptom resolution in SARS-CoV-2 seronegative subjects who develop COVID-19 disease.
7. Evaluate the humoral immune response to INO-4800 in subjects who are SARS-CoV-2 seronegative at baseline	7a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody titers in subjects who are SARS-CoV-2 seronegative at baseline 7b. Incidence of seroconversion by SARS-CoV-2 Spike glycoprotein antigen specific binding antibody assay in subjects who are SARS-CoV-2 seronegative at baseline
Exploratory Objectives	**Associated Exploratory Endpoints**
1. Evaluate the expanded immunological profile by assessing both T and B cell immune responses	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot. 1b. T cell phenotype (i.e., Th1/Th2/Th17) analysis by mRNA expression levels or flow cytometry may be conducted. The humoral response may also be interrogated by such assays as neutralization, ADCC or B cell ELISpot to further delineate the functional nature of the humoral response.

Efficacy Assessment:

Subjects will receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls

throughout the study. Subjects will be regularly tested for SARS-CoV-2 infection using saliva and serologic testing. If COVID-19 disease is suspected based on symptoms and laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptoms that begin on or after 14 days post-dose 2 with laboratory confirmation will contribute to the case count for the primary endpoint analysis.

Safety Assessment:

Subjects will be followed for safety during the entire duration of trial participation. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization.

Baseline and serial laboratory blood and urine samples will be drawn according to the Schedule of Events (Table 2). Subjects will report any potential symptoms of COVID-19 in real time during the trial and will be followed bi-weekly through clinic visits or phone calls.

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 2). Binding ELISA will be evaluated at serial timepoints. All subjects will be tested for seroconversion as indicative of vaccine-take. Furthermore, the Spike-Binding ELISA results will be assessed in order to determine antibody correlates of protection. In addition, immune assessments will be conducted to determine additional correlates of protection. The correlate can either be mechanistic or non-mechanistic. Determination of assays, timepoints and number of subjects tested will be based on current literature and reagent availability.

Clinical Trial Population:

Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years or older.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, physical examination and vital signs performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working, visiting or residing in an environment with high risk of exposure to SARS-CoV-2 (e.g., civilian and military health care workers or emergency response personnel having direct interactions with patients or providing direct care to patients, nursing home staff);
f. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
g. Body Mass Index of 18-30 kg/m^2 at Screening;
h. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening (subjects who are positive for Hepatitis C antibody but are in remission as defined by undetectable HCV RNA level ≥ 12 weeks after completion of HCV therapy may be enrolled)
i. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;

- Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
- Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
  - hormonal contraception including implants, injections or oral;
  - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
  - abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the screening visit until 3 months following the last dose;
c. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
d. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0;
e. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS;
f. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring medical evaluation and/or treatment within the past 5 years;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, resting systolic blood pressure >150 mm Hg or a resting diastolic blood pressure >95 mm Hg at Screening;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 7.0%);
   - Malignancy within the past 5 years, with the exception of superficial skin cancers that only required local excision;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring medical evaluation and/or treatment within the past 5 years;
   - History of seizures within the past 5 years with the use of no more than a single antiepileptic agent;
g. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies;
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
   - Current or anticipated use of 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);

- History of solid organ or bone marrow transplantation;
- History of receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

h. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

i. Blood donation within 1 month prior to Day 0;
j. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
k. Reported ongoing smoking or vaping;
l. Reported alcohol or substance abuse/dependence within the past 5 years;
m. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Investigational Product: A single 1.0mg ID injection of INO-4800 (~0.1mL dose volume) followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Placebo: A single ID injection of SSC-0001 (~0.1mL) followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate (SSC) buffer, refrigerated.

TABLE 2 - SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Wk 1	Wk 4		Tel #1	Wk 6	Wk 8	Tel #2	Wk 12	Tel #3-6	Wk 22	Tel #7-9	Wk 30	Tel #10-12	Wk 38	Tel #13-15	Wk 46	Tel #16-19	Wk 56	Illness
	Screen[a]	Day 0		Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±3d)	Day 56 (±3d)	Phone call - Day 70 (±5d)	Day 84 (±5d)	Phone calls Days 98, 112, 126, 140 ±5d)	Day 154 (±5d)	Phone calls Days 168, 182, 196 (±5d)	Day 210 (± 10d)	Phone calls Days 224, 238, 252 (±5d)	Day 266 (± 10d)	Phone calls Days 280, 294, 308) (±5d)	Day 322 (± 10d)	Phone calls Days 336, 350, 364, 378 (±5d)	Day 393 (± 10d)	Suspected COVID-19 assessment visit[n]
		Pre	Post		Pre	Post																
Informed Consent	X																					
Inclusion/Exclusion Criteria	X																					
Medical history	X	X[a]																				
Demographics	X																					
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X		X	X			X	X		X		X		X		X		X		X	X
Vital Signs	X	X		X	X			X	X		X		X		X		X		X		X	X
Height and Weight	X																					
CBC with differential	X			X				X			X		X		X		X		X		X	X
Chemistry[c]	X			X				X			X		X		X		X		X		X	X
SARS-CoV-2 Serology[d]	X	X		X			X	X	X		X		X		X		X		X		X	X
HIV, HBV, HCV Serology	X																					
Urinalysis Routine[e]	X			X				X			X		X		X		X		X		X	X
Pregnancy Test[f]	X	X			X																X	
INO-4800 or Placebo + EP[g]		X			X																	
Download EP Data[h]			X			X																
Adverse Events[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Responses[j]		X			X			X	X		X		X		X		X		X		X	X
Humoral Responses[k]		X			X			X	X		X		X		X		X		X		X	X
SARS-CoV-2 RT-PCR (Saliva)[l]	X	X		X	X		X	X	X		X		X		X		X		X		X	X[m]

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at screening and Day 393 (or any study discontinuation visit). Targeted physical exam at all other visits.
c. Includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin, and hemoglobin A1c (hemoglobin A1c collected at screening only).
d. SARS-CoV-2 antibody.
e. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.

f. Serum pregnancy test at screening. Urine pregnancy test at other visits.
g. An intradermal injection in skin preferably over deltiod muscle followed by EP at Day 0 and Day 28.
h. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
i. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
j. Cellular responses utilizing ELIspot assay requires 34 mL of whole blood; collect 8.5 mL of whole blood in each of four 10 mL Acid Citrate Dextrose (ACD, Yellow top) tubes per time point. Note: Collect a total of 68 mL whole blood prior to 1st dose.
k. Humoral responses utilizing the S-Binding ELISA, NP-Binding ELISA and SARS-CoV-2 neutralization assays require a total of 8.5 mL of serum collected in a 10-mL red top serum collection tube per time point. Note: Collect four aliquots of 1 mL each (total 4 mL) serum at each time point prior to 1st dose (Screening and prior to Day 0 dosing).
l. SARS-CoV-2 RT-PCR with saliva specimen; The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.
m. Nasopharyngeal, oropharyngeal swabs and saliva specimens.
n. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The laboratory-confirmation of a case will be based on SARS-CoV-2 RT-PCR. Additional safety testing will be collected to understand the impact on various organ systems. Additional diagnostic testing (e.g., influenza diagnostics) may be ordered at the discretion of the Investigator.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to US and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

The lack of available therapy in conjunction with increasing numbers of global cases indicate that SARS-CoV-2 infection remains a serious unmet medical concern. Appropriate measures to prevent, control and treat existing and future infections are in dire need.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [1-3]. These cases were announced on January 6, 2020 as testing negative for influenza, SARS, and MERS. On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named “Wuhan-Hu-1.” The gene sequence of that isolate was then generated and determined to be of a novel coronavirus[4, 5]. That gene sequence was publically posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [6, 7], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, “COVID-19,” associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The cluster of human cases first identified pneumonia of unknown origin infections was comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting an animal as the source of the novel virus transmission to humans.

The first U.S. case of COVID-19 was detected in Washington State, confirmed on and as announced January 21, 2020 by the Washington State Department of Health and the U.S. Centers for Disease Control and Prevention (US CDC) [8]. That was a case of a traveler who had returned from Wuhan, China. Since that case detection, human-to-human local transmission began (or continued from previously undetected infections) in the U.S., and as of May 17, 2020, nearly 1.5 million lab-confirmed US COVID-19 cases and nearly 90,000 US deaths due to COVID-19 have been reported [9]. COVID-19 cases have been reported from all 50 states and several territories.

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) infectious agents in a growing number of coronaviruses which have evolved to infect humans. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and then progressed to be declared on March 11, 2020 as a pandemic [10], associated with substantial morbidity and mortality [11]. The pandemic of COVID-19 includes scope of lab-confirmed cases reported by virtually all countries and COVID-19 deaths reported by many of those countries. As of May 17, 2020, a total of over 4.7 million lab-confirmed COVID-19 cases have been reported internationally, including nearly 315,000 deaths [9]. However, and very importantly, because this is from a new pathogen and thus lab testing and reporting are not widely

available and thus incomplete, the true number of cases of COVID-19 is likely far higher than reported, and the true number of SARS-CoV-2 infections – regardless of disease – is thought to be many (perhaps dozens of) times the number of detected infections and reported COVID-19 cases.

An article in *JAMA* by Wu and McGoogan [12] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [13]. That report found that among a total of 72,314 case records, 44,672 were classified as confirmed cases of SARS-CoV-2 infection (62%; diagnosis based on positive viral nucleic acid test result on throat swab samples), 16,186 as suspected cases (22%; diagnosis based on symptoms and exposures only, no test was performed because testing capacity was insufficient to meet current needs), 10,567 as clinically diagnosed cases (15%; this designation is being used in Hubei Province only; in these cases, no test was performed but diagnosis was made based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia), and 889 as asymptomatic cases (1%; diagnosis by positive viral nucleic acid test result but lacking typical symptoms including fever, dry cough, and fatigue) [14]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [14]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Because of the novelty of SARS-CoV, the COVID-19 it causes and the serious outcomes in some patients, and the speed of propagation worldwide, unsurprisingly there has been an explosion of epidemiological, clinical, virological, and other data have emerged from China, the United States, and many other countries about this new virus and disease. These data in summary have further established that 1) SARS-CoV-2 is transmitted person-to-person [15], even from those asymptomatic or presymptomatic [16-18], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.5 to 6.49, with a mean average of 3.28 and a median average of 2.79 [19], 3) the constellation of symptoms, signs, and an incubation period range of 2 to 14 days [20], and 4) the asymptomatic proportion of those infected being substantial, perhaps 50% or even up to 80% [15, 21, 22]. Further, research has found that the risk of death from COVID-19 increases with age and for those with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned case-fatality ratio and similar estimates are from crude analyses that have only or largely been of moderate to serious cases and not included minor cases that did not present to health care. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [3] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5 12%) and secondary infection (n=4, 10%).

Transmission of SARS-CoV-2 occurred mainly after days of illness [23] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [24]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [25] and appears different from that seen in patients infected with SARS-CoV [24]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [18].

T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of the counts of total T cells, and $CD4^+$and $CD8^+$ T cell subsets, as well as serum cytokine concentration based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection, admitted into two hospitals in Wuhan from December 2019 to January 2020, and 40 healthy controls in the same two hospitals receiving routine physical examination. The number of total T cells, and $CD4^+$ and $CD8^+$ T cells were dramatically reduced in COVID-19 infected patients, especially among elderly patients (≥60 years of age) and in patients requiring Intensive Care Unit (ICU) care. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells lower than 800/μL, 300/μL, or 400/μL, respectively, are negatively correlated with patient survival [26].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Hospitals can provide supportive care for infected people. Currently, no licensed preventative vaccine or anti-viral therapy is available as indicated for SARS-CoV-2 infection or COVID-19, except for Emergency Use Authorization (EUA). Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated. Remdesivir has received Emergency Use Authorization for treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease [27]. Chloroquine Phosphate also has received EUA for treatment of adults and adolescents who are hospitalized with COVID-19 for whom a clinical trial is not available [28]. Hydroxychloroquine, with and without azithromycin, is being investigated in multiple clinical trials, as is plasma-derived polyclonal antibodies and immune globulin, among other therapies.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. No specific treatment for COVID-19 is currently available, thus highlighting the need for effective therapeutic and preventive solutions. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat existing and future infections.

To address this critical need for a medical countermeasure for prevention of further dissemination of SARS-CoV-2, we have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and the possibility of leveraging established regulatory pathways to the clinic. Furthermore, this technology has demonstrated proof of concept efficacy and safety in humans in a phase 2b randomized, double-blind, placebo-controlled study [29], for human papillomavirus (HPV) associated cervical pre-cancer and is currently in two multinational phase 3 trials for that indication (NCT03185013 and NCT03721978) and several phase 2 trials for related and other indications. For the development of a SARS-COV-2 vaccine candidate, we have built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine. In a phase 1 clinical study, the MERS-CoV coronavirus vaccine was well tolerated and immune response was induced in more than 85% of participants after two vaccinations, and durable through 1 year of follow-up [30].

1.3.1 DOSE AND REGIMEN RATIONALE

The intended use for INO-4800 is for both routine prophylaxis and use during an outbreak situation. As such, there is a desire to demonstrate the ability of the vaccine to drive immune responses within 4-8 weeks of administration, which supports evaluation of a dose regimen that includes Day 0 and Day 28.

In this study, 1.0 mg of vaccine is administered by ID injection and followed by EP at Day 0 and Day 28. The dose selection is supported by the well tolerated safety profile in the phase 1 trial of INO-4800 (COVID19-001, NCT04336410) as well as our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17].

In the ongoing phase 1 study of INO-4800, as of May 18, 2020, a total of 40 subjects has been enrolled into the phase 1 study, 20 subjects each in 1.0 mg and 2.0 mg groups. All subjects received at least one dose of INO-4800 while nine subjects in 1.0 mg group completed two doses of vaccination. A total of six adverse events (AEs) has bene reported as shown in Table 2. All of the AEs are grade 1 AEs. No serious adverse events (SAEs) or adverse event of special interest (AESIs) have been reported. Two meetings of the DSMB have been convened. After thorough review of available safety laboratory data and AE list, the DSMB did not find any safety concerning and recommended the trial continue without modification.

Seropositive subjects are also included in the study to assess safety of INO-4800 in those with prior exposure to SARS-CoV-2 infection.

1.3.2 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B and T-cell responses, stability of the vaccine across a

broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [31-40]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, Middle East Respiratory Syndrome (MERS) coronavirus, rabies virus, Severe Acute Respiratory Syndrome (SARS) coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [39, 41]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [42]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [43].

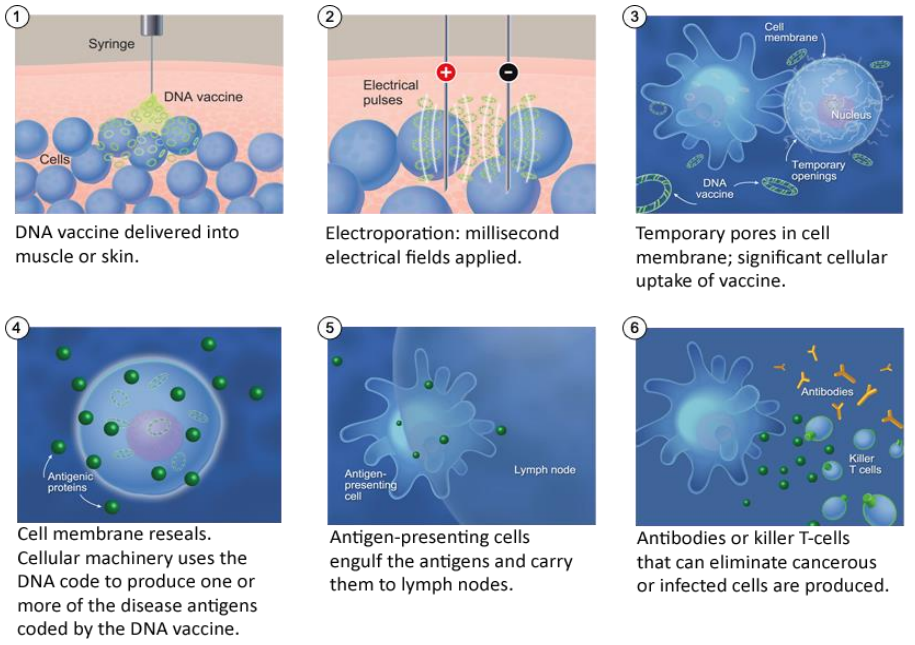
Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [44]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.3 USE OF ELECTROPORATION WITH DNA VACCINES

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 1). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [45]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens [45] for the activation of both cellular and humoral responses [46, 47]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [47]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [48, 49].

The Inovio Pharmaceuticals' constant current EP device [45] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device will be used in this clinical trial. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [50].

Figure 1: How Electroporation Works in the Body



1.4 POTENTIAL BENEFITS AND RISKS

As of May 18, 2020, a total of 40 subjects have been dosed with INO-4800 ID. In the ongoing phase 1 study of INO-4800 administered ID followed by EP using CELLECTRA™ 2000 devices in healthy volunteers the most frequently reported AE has been injection site reactions, and all AEs have been Grade 1.

No specific AE has been identified as a risk. There may be potential benefit for prevention of COVID-19 disease, but efficacy is still unknown. Data gathered in this trial will be useful for future development of this prophylactic vaccine against SARS-CoV-2 infection.

Additional details regarding the benefits and risks for subjects participating in this clinical trial may be found in the Investigator's Brochure (IB).

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety and efficacy of INO-4800 for future development.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP using CELLECTRA® 2000 will provide protection against laboratory-confirmed COVID-19 in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is a Phase 3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800 (1.0mg), administered by intradermal

(ID) injection followed immediately by electroporation (EP) using CELLECTRA® 2000 device using a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objective of this trial is to evaluate the efficacy of INO-4800 in seronegative subjects.

Approximately 3438 seronegative subjects and 100 seropositive subjects 18 years of age or older are expected to be enrolled and will be randomized at a 1:1 ratio to receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001). See Table 1.

Table 2: COVID19-311 Dose Groups

Study Group	Expected Number of Seronegative Subjects	Number of Seropositive Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	Total Dose
INO-4800	1719	50	0, 28	1	1.0 mg	2.0 mg
Placebo	1719	50	0, 28	1	0	0
Total	3438	100				
Grand Total	3538					

The trial is case-driven. Among seronegative subjects, a total of 89 observed cases will be required for 90% power to declare the vaccine efficacious (>15%), assuming a true efficacy of 60%. A sample size of 3438 seronegative subjects is expected to be required to achieve this number of cases assuming an underlying attack rate of 3.7%. The sample size may be increased if the underlying attack rate is lower than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 6-months post-dose 2. Subjects will be followed for 12 months post-dose 2.

All subjects, investigating site staff (excluding site pharmacy staff) and the Sponsor will be blinded throughout the trial. A group-level unblinding will occur when all subjects' data is complete for the primary efficacy timeframe.

A Data Safety Monitoring Board (DSMB) will convene regularly throughout the trial to review unblinded safety data and adjudicate the cases of COVID-19 disease. Details of its scope will be provided in a charter.

3.1 PRIMARY OBJECTIVES

See Table 3.

3.2 PRIMARY ENDPOINTS

Table 3: Primary Objective and Associated Endpoints

Primary Objective	Associated Primary Endpoints
1. Evaluate the efficacy of INO-4800 in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of laboratory-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline

3.3 SECONDARY OBJECTIVES

See Table 4.

3.4 SECONDARY ENDPOINTS

Table 4: Secondary Objectives and Associated Endpoints

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of Injection site reactions 1b. Incidence of systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of injection site reactions, systemic AEs by SOC, PT, severity and relationship to investigational product, SAEs, and AESIs in subjects who are SARS-CoV-2 seropositive at baseline
2. Evaluate the efficacy of INO-4800 of laboratory-confirmed severe or critical COVID-19 cases for 6 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of severe or critical COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 2b. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects requiring mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2 2c. Incidence of deaths due to COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2
3. Evaluate the efficacy of INO-4800 with respect to SARS-CoV-2 infections who are SARS-CoV-2 seronegative at baseline	3. Incidence of laboratory-confirmed SARS-CoV-2 infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2
4. Evaluate efficacy of INO-4800 for 12 months post-dose 2 in subjects who are SARS-CoV-2 seronegative at baseline	4a. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days post-dose 1 until Day 42 4b. Incidence of severe or critical COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until End of Study (EOS) 4c. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects requiring mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery starting 14 days after completion of the 2-dose regimen until EOS 4d. Incidence of deaths due to COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14

	days after completion of the 2-dose regimen until EOS 4e. Incidence of laboratory-confirmed SARS-CoV-2 infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
5. Evaluate the short-term efficacy of INO-4800 following one dose in subjects who are SARS-CoV-2 seronegative at baseline	5. Incidence of COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days post-dose 1 until 14 days post-dose 2
6. Evaluate the timing of symptom resolution in subjects who develop COVID-19 illness who are SARS-CoV-2 seronegative at baseline	6. Days to symptom resolution in SARS-CoV-2 seronegative subjects who develop COVID-19 disease.
7. Evaluate the humoral immune response to INO-4800 in subjects who are SARS-CoV-2 seronegative at baseline	7a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody titers in subjects who are SARS-CoV-2 seronegative at baseline 7b. Incidence of seroconversion by SARS-CoV-2 Spike glycoprotein antigen specific binding antibody assay in subjects who are SARS-CoV-2 seronegative at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 5.

3.6 EXPLORATORY ENDPOINT

Table 5: Exploratory Objectives and Associated Endpoints

Exploratory Objectives	Associated Exploratory Endpoints
1. Evaluate the expanded immunological profile by assessing both T and B cell immune responses	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot. 1b. T cell phenotype (i.e., Th1/Th2/Th17) analysis by mRNA expression levels or flow cytometry may be conducted. The humoral response may also be interrogated by such assays as neutralization, ADCC or B cell ELISpot to further delineate the functional nature of the humoral response.

3.7 EFFICACY ASSESSMENT

Subjects will receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be followed for the duration of the trial by regularly scheduled clinic visits and phone calls. Subjects will be routinely tested for SARS-CoV-2 using saliva and serologic testing. If COVID-19 disease is suspected based on symptoms or testing, site personnel will arrange for a clinic visit. Subjects with symptoms that begin on or after 14 days post-dose 2 with laboratory confirmation will contribute to the case count for the primary endpoint analysis. The DSMB will adjudicate each case of laboratory-confirmed COVID-19 disease for inclusion in the primary efficacy analysis (see Section 12.1).

3.7.1 CASE DEFINITION FOR LABORATORY-CONFIRMED COVID-19 DISEASE:

Case Definition for Mild COVID-19

- Positive testing by standard RT-PCR assay;
- Symptoms of mild illness with COVID-19 that could include fever, cough, chills, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain, new loss of taste or smell, without shortness of breath or dyspnea;
- No clinical signs indicative of Moderate, Severe, or Critical Severity (see below).

Case Definition for Moderate COVID-19

- Positive testing by standard RT-PCR assay;
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion;
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 but < 30 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 but < 125 beats per minute;
- No clinical signs indicative of Severe or Critical Illness Severity.

Case Definition for Severe COVID-19

- Positive testing by standard RT-PCR assay;
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress;
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300;
- No criteria for Critical Severity.

Case Definition for Critical COVID-19

- Positive testing by standard RT-PCR assay;
- Evidence of critical illness, defined by at least one of the following:
  - Respiratory failure defined based on resource utilization requiring at least one of the following:
    - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
  - Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors);
  - Multi-organ dysfunction/failure.

Case Definition for Suspected COVID-19 Disease

- Unavailable, inclusive or negative testing by standard RT-PCR assay without an opportunity for testing or retesting;
- Recent seroconversion by NP-Binding ELISA or CT scan evidence of COVID-19;
- Clinical symptoms and signs indicative of mild, moderate, severe or critical COVID-19.

3.7.2 CASE DEFINITION OF "LABORATORY-CONFIRMED SARS-COV-2 INFECTION"; SARS-COV-2 INFECTION WITHOUT SYMPTOMS

- Positive testing by standard RT-PCR assay;
- No clinical signs and symptoms.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the entire duration of trial participation. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization.

Baseline and serial laboratory blood and urine samples will be drawn according to the Schedule of Events (Table 2). Subjects will report any potential symptoms of COVID-19 in real time during the trial and subjects will be followed bi-weekly by visit or phone call.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 2). Binding ELISA will be evaluated at serial timepoints. All subjects will be tested for seroconversion as indicative of vaccine-take. Furthermore, the Spike-Binding ELISA results will be assessed in order to determine antibody correlates of protection. In addition, immune assessments will be conducted to determine additional correlates of protection. The correlate can either be mechanistic or non-mechanistic. Determination of assays, timepoints and number of subjects tested will be based on current literature and reagent availability.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, physical examination and vital signs performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working, visiting or residing in an environment with high risk of exposure to SARS-CoV-2 (e.g., civilian and military health care workers or emergency response personnel having direct interactions with patients or providing direct care to patients, nursing home staff);
f. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
g. Body Mass Index of 18-30 kg/m^2 at Screening;
h. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at

screening (subjects who are positive for Hepatitis C antibody but are in remission as defined by undetectable HCV RNA level ≥ 12 weeks after completion of HCV therapy may be enrolled)

i. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the screening visit until 3 months following the last dose;
c. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
d. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0;
e. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS;
f. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring medical evaluation and/or treatment within the past 5 years;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, resting systolic blood pressure >150 mm Hg or a resting diastolic blood pressure >95 mm Hg at Screening;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 7.0%);
   - Malignancy within the past 5 years, with the exception of superficial skin cancers that only required local excision;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring medical evaluation and/or treatment within the past 5 years;
   - History of seizures within the past 5 years with the use of no more than a single antiepileptic agent;
g. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies;

- Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
- Current or anticipated use of 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);
- History of solid organ or bone marrow transplantation;
- History of receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

h. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

i. Blood donation within 1 month prior to Day 0;
j. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
k. Reported ongoing smoking or vaping;
l. Reported alcohol or substance abuse/dependence within the past 5 years;
m. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 2) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up

visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
    - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Sterile saline sodium citrate (SSC) buffer (SSC-0001), which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps, will be used as the placebo.

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 vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering current controlled electrical pulses as follows:

- An EP treatment consists of four pulses.
- An Array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue.
- Voltage levels are limited to 200 volts (V) for patient safety.
- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device for ID administration is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles.

5.2 DOSING REGIMENS

- Investigational Product: A single 1.0mg ID injection of INO-4800 (~0.1mL dose volume) followed immediately by EP administered at Day 0 and Day 28 (±3 days)
- Placebo: A single ID injection of SSC-0001 (~0.1mL) followed immediately by EP administered at Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is double-blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel will be blinded throughout the trial. There is no difference in appearance for both the INO-4800 product and the placebo; however, they are packaged in different sized vials. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

The PI may request to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is essential for proper clinical management of the subject, as judged by the PI. It is preferred, but not required, that the PI first contact the Medical Monitor (MM) to discuss options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the Investigator's Brochure (IB).

5.3.2 **CELLECTRA® 2000**

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 **HANDLING AND STORAGE**

5.4.1 **INO-4800 AND PLACEBO**

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, it must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 **CELLECTRA® 2000**

See User Manual for operating and storage conditions.

5.5 **PREPARATION AND DISPENSING**

INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a participant is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 **USE OF STUDY DEVICE**

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

The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training from Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigative site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Table 2.) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also 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 30 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 30 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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics and document any ongoing, pre-existing conditions;
- Collect adverse events (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examinations (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing, HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C serology (Section 6.4) per national guidelines;
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or occurred within the 12 weeks prior to Screening. 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. Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (investigational product or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Review restrictions for injection and EP (Section 6.4.8);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Randomize subject (instructions to be provided under separate cover).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new adverse events (Section 6.4.4);
- Download EP Data (Section 6.4.1.1).

6.1.2.2 Day 7 and Day 42 (post-dose visits)

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);

- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

6.1.2.3 Phone calls (Days 35, 70, 98, 112, 126, 140, 168, 182, 196, 224, 238, 252, 280, 294, 308, 336, 350, 364, and 378)

Phone calls to subjects have been spaced bi-weekly between study visits for the duration of the trial. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); only SAEs, AESIs and MAAEs will be collected after the Day 56 Visit;
- Arrange on-site visit if there are any signs and symptoms of COVID-19 disease;
- Record current concomitant medications/treatments (Section 6.4.7);
- Remind subject to self-collect saliva sample and ship to designated laboratory (Section 6.4.9).

6.1.2.4 Day 56 Visit

The following evaluations will be performed at this visits:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);

6.1.2.5 Days 84, 154, 210, 266, 322 Visits and Day 393 Visit

The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); SAEs, AESIs, and MAAEs will be collected at these visits.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Days 84, 154, 210, 266, 322) or full physical examination (Day 393, EOS) (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test at Day 393 visit only (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);

- Collect urine for routine urinalysis (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);

6.1.2.6 Suspected COVID-19 Assessment Visit

Subjects will be evaluated during a "Suspected COVID-19 assessment visit" when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The laboratory-confirmation of a case will be based on SARS-CoV-2 RT-PCR. Additional safety testing will be collected to understand the impact on various organ systems. Additional diagnostic testing (e.g., influenza diagnostics) may be ordered at the discretion of the Investigator. The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); Only SAEs, AESIs and MAAEs will be collected at visits after Day 56;
- Document any present conditions and concomitant illnesses;
- Record clinical signs and symptoms;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect nasopharyngeal, oropharyngeal swabs and saliva for SARS-CoV-2 RT-PCR detection.

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects
- Explain the clinical trial
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description
  - Eligibility criteria for entering the clinical trial
  - Clinical trial treatments and follow-up procedures description
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives
    - Potential benefits and risks
    - Discomforts/inconveniences
    - Subject's rights and responsibilities

The subject or subject's legally authorized representative is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject or subject's legally authorized representative. The qualified clinical trial personnel will document the process of obtaining informed consent within the source

record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30 day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a four digit site code and a four digit subject number starting with 0001. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the Case Report Form (CRF).

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Table 2).

HEIGHT AND WEIGHT

Weight (kg) and height (cm) will be collected at Screening.

LABORATORY EVALUATIONS

At Screening and at visits specified in the Schedule of Events (Table 2), blood samples will be collected for safety assessments. Approximately 680 mL of blood will be drawn from each subject over the course of the study. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 at visits specified in the Schedule of Events (Table 2).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, BUN (blood urea nitrogen), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, total bilirubin (TBili), and hemoglobin A1c at Screening and at visits specified in the Schedule of Events (Table 2). Hemoglobin A1c will only be performed at Screening.

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and at visits specified in the Schedule of Events (Table 2). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

Antibodies to Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and HIV antibody or rapid test will be measured at Screening only. Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Table 2).

Pregnancy Testing:

For women of child bearing potential (WOCBP), a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit. 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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy.

6.4.1 INJECTION AND EP

Subjects will receive a two-dose regimen of INO-4800 or placebo by ID injection in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28.

Only if the deltoid area is not a suitable location (see exclusion criterion 'f'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry and hematology and urinalysis will be performed at the visits listed in the Schedule of Events (Table 2) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued in September 2007 (Appendix A). Laboratory values that are not clinically significant (NCS) in the Investigator's opinion will not be reported as adverse events.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

Subjects will be queried regarding the occurrence of any adverse events including adverse events related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All adverse events will be captured from the time of the informed consent until 28 days post-dose 2. Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

The IP administration procedure consists of an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of the electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug. Consequently, reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 6 below) and use the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (Appendix A). Administration (injection) site reactions and administration site pain will be evaluated starting 30 minutes following injection/EP. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 6: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

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

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

[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 PERIPHERAL BLOOD IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at specified in the Schedule of Events (Table 2) for cellular and humoral immunology assessments. Baseline (Day 0)

immunology samples are required to enable all immunology testing. Therefore a total of 68mL whole blood and 8mL serum is required prior to 1st dose. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual. The T and B cell immune responses to INO-4800 will be measured using assays that include but are not limited to ELISA, neutralization, assessment of immunological gene expression, assessment of immunological protein expression, flow cytometry and ELISPOT. In addition, humoral responses to SARS-CoV-2 Nucleocapsid Protein (NP) may also be assessed to rule out potential infection by wild-type SARS-CoV-2 post INO-4800 treatment during the trial. Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the trial.

6.4.7 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) must be recorded on 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.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor.

The decision to administer a prohibited medication/treatment (Section 6.4.8) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.8 RESTRICTIONS

Subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature >38.0 degrees Celsius or 100.4 degrees Fahrenheit) within 72 hours prior to each dosing.

Subjects should refrain from donating blood from Screening visit through the duration of the trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.9 SARS-CoV-2 TESTING

Serology SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 2: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on saliva specimens collected at Screening and during study visits (see Table 2: Schedule of Events) with bi-weekly home self-collections, when possible, between study visits. The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.

If either the SARS-CoV-2 antibody or RT-PCR test result is positive during the trial, the subject will be notified of the result and will be requested to come to the clinic for an evaluation. During that visit, a blood sample will be collected for serologic testing and 3 specimens (nasopharyngeal swab, oropharyngeal swab and saliva) will be collected to detect SARS-CoV-2 using the RT-PCR assay. If acute SARS-CoV-2 infection is diagnosed regardless of symptoms, serial saliva samples will be collected every 2 days for 20 days for quantitative SARS-CoV-2 RT-PCR testing to assess the viral load..

6.4.10 COVID-19 DISEASE MONITORING

All subjects will be monitored through regularly scheduled clinic visits and phone calls for the development of symptoms suggestive of COVID-19 disease. Site personnel will arrange for a clinic visit for subjects reporting symptoms suggestive of COVID-19 (e.g., fever, cough, chills, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain, shortness of breath or dyspnea, New loss of taste or smell)) at any time during the study. During that visit, a blood sample will be collected for serologic testing and 3 specimens (nasopharyngeal swab, oropharyngeal swab and saliva) will be collected to detect SARS-CoV-2 using the RT-PCR assay. Diagnosis of COVID-19 will be made by the investigator according to the case definitions (See Section 3.7.1) and recorded on the CRF.

If the specimens are RT-PCR negative, a diagnosis of influenza has been ruled out, and COVID-19 remains a possible diagnosis, the RT-PCR assay may be repeated. Furthermore, SARS-CoV-2 RT-PCR detection may be performed on sputum, endotracheal aspirate or bronchoalveolar lavage samples, if available. Pulmonary CT scan findings showing typical interstitial pneumonia including ground-glass opacities may corroborate the diagnosis of COVID-19 disease. The formal radiologist's interpretation of the CT scan should be included as a source document. Diagnosis of COVID-19 will be made by the investigator according to the case definitions (See Section 3.7.1) and recorded on the CRF. If SARS-CoV-2 infection or COVID-19 is diagnosed, saliva samples will be collected every 2 days for 20 days for SARS-CoV-2 RT-PCR testing.

Subjects with a confirmed COVID-19 diagnosis after dose 1 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Recovery from COVID-19 disease requires resolution of clinical symptoms and a minimum of two consecutive negative nasopharyngeal swabs collected at least 24 hrs apart..

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued September 2007 (Appendix A).

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 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 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)

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
- 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
- Laboratory-confirmed COVID-19 disease

7.2.1 LABORATORY-CONFIRMED COVID-19 DISEASE AND SEVERE COVID-19 DISEASE

The DSMB will adjudicate COVID-19 cases. Details are provided in the DSMB Charter. The endpoint of laboratory-confirmed COVID-19 disease and severe COVID-19 disease is recorded in the CRF. The endpoint is not recorded as an AE or SAE.

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.
- COVID-19 disease with an outcome of death is recorded as an endpoint, and not recorded as an SAE.
- 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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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, preferred term, severity and causal relationship to clinical trial treatment
- Changes in laboratory parameters
- Local and systemic injection site review; special attention will be paid to the examination of the injection site

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix B are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

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 further administration of the investigational product in the clinical trial
- 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment.
- Any Grade 4 adverse events related to study treatment.
- Any report of anaphylaxis related to study treatment.

The Medical Monitor, in consultation with the Safety Review Committee members when necessary, will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an emergency meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor of the Sponsor. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed tosafety.inovio@apcerls.co or faxed to [redacted]. The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 4: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 5: Medical Monitor Direct contact Information

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

All SAEs, treatment-related AEs and AESIs must be followed by the PI until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 number (SID)
- Investigational product(s) (IP) and/or study device
- Investigator causal relationship to the IP(s) and/or study 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 SAE 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 previous signs and/or symptoms will be subsumed 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 Toxicity Grading Scale for Healthy Adult and Adolescent

Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration [FDA] Guidance for Industry) (Appendix A).

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 prior to 3 months following the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose 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 dose administrations, 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. 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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)/RESEARCH ETHICS BOARDS (REBS)/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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy

7.14 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.15 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of laboratory-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 6 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 15%). Secondary efficacy analyses involve severe cases, cases requiring mechanical ventilation, cases resulting in death, long-term efficacy (disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2), short-term efficacy (disease starting 14 days after 1 dose

until 14 days post-dose 2), and timing of symptom resolution. Other secondary analyses concern safety and humoral immunological measures. Exploratory analyses concern cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Among baseline seronegative subjects, the primary hypothesis of relative efficacy greater than 15% will be tested with H_0: $p \geq .85/(.85+k)$ *vs.* H_1: $p < .85/(.85+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all baseline seronegative subjects who receive all doses of Study Treatments and have no protocol violations. Subjects with disease occurring prior to 14 days post-dose 2 will be excluded from the PP population. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population will be primary for the analysis of efficacy in this trial.

The modified intention to treat (mITT) population includes all baseline seronegative subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analysis of efficacy.

The intention to treat (ITT) population includes all baseline seronegative subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be considered supportive for the corresponding PP population for the analysis of efficacy.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY EFFICACY ANALYSIS

Among baseline seronegative subjects, the primary hypothesis of relative efficacy greater than 15% will be tested with H_0: $p \geq 0.85/(0.85+k)$ *vs.* H_1: $p < 0.85/(0.85+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI for efficacy exceeds 15%.

For calculating k, an individual subject's follow-up time is either:

a) the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or

b) the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters (t, p=λv/(λv+λc)). The relationship between p and efficacy is: efficacy = (1-(1+k)p)/(1-p). Therefore, testing efficacy > 15% corresponds to testing p < 0.85/(0.85+k). Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 6 months after Dose 2. Subjects identified as cases based on symptoms starting prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values. The efficacy timeframe is different for the long-term efficacy endpoint and for the short-term efficacy endpoint. For the long-term endpoint, the end of the timeframe is 12 months postdose 2, and for the short-term endpoint, the start of the timeframe is 14 days postdose 1 and the end of the timeframe is 14 days postdose 2.

The secondary efficacy endpoint regarding timing of symptom resolution will be analyzed with Kaplan-Meier plots by treatment group.

8.5.2.2 Immunogenicity

Among baseline seronegative subjects, post-baseline antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean titers and associated 95% CIs.

Among baseline seronegative subjects, post-baseline seroconversion from ELISA will be compared between treatment groups using differences in proportions and associated Miettinen and Nurminen 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for immunogenicity analyses.

8.5.3 SAFETY ANALYSES

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will also be stratified by baseline seronegative versus seropositive status.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.3.3 Physical Examination

The percentage of subjects with abnormal physical examination findings at each time point will be summarized by treatment arm and by body system, for the Safety population. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.4 **DISPOSITION**

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.5 **DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS**

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.5.2 Medical History

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT and PP populations. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.5.3 Prior Medications

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 by treatment arm, for the Mitt and PP populations. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.5.6 INTERIM ANALYSES

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

A group-level unblinded (INO-4800, Placebo) summary and analysis of efficacy will be produced once the primary endpoint 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 56 visit. The summary and analysis will allow the Sponsor to have results with respect to the primary endpoint on which to make decisions regarding the INO-4800 program, while still gathering long-term data through the final Week 56 visit. This summary/analysis will not be provided if the total count of subjects who experience the event of interest is greater than 0 and the count for a treatment group relative to this total count is less than 3%. The group-level unblinded (INO-4800, Placebo) production of the summary and analysis will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), which will also be 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.

8.5.7 MULTIPLICITY

Not applicable; there is one hypothesis that will be tested.

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Immunogenicity

Among baseline seronegative subjects, post-baseline Increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using a difference in medians and associated non-parametric 95% CIs.

Among baseline seronegative subjects, T cell phenotype and functional nature of the humoral response results will be compared between treatment groups using a difference in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for immunogenicity analyses.

8.5.9.2 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will also be stratified by baseline seronegative versus seropositive status.

8.6 SAMPLE SIZE/POWER

The trial is case-driven. Among baseline seronegative subjects, a total of 89 observed cases will be required to provide 90% power to declare the vaccine efficacious (>15%), utilizing the methodology described in Section 8.5.1 and assuming a true efficacy of 60%. A sample size of 3438 seronegative subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

A group of 100 baseline seropositive subjects will also be enrolled.

8.7 RANDOMIZATION AND BLINDING

Subjects will be randomized (1 INO-4800:1 Placebo) in a stratified manner according to baseline serostatus.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of participants to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

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

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

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

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor and 2 additional physicians, will review blinded safety and tolerability data on a

regular basis throughout the trial until the trial is unblinded. The SRC will meet approximately once per month, at a minimum.

The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
    - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
    - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
    - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
    - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
    - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
    - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor. Clinical trial insurance has been taken out according to 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 per 21 CFR Part 54.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bGH polyA	Bovine growth hormone 3' end poly-adenylation signal
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCO_3	Biocarbonate
hCMV	Human CMV
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
K	Potassium
KanR	Kanamycin resistance gene
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NIAID	National Institute for Allergy and Infectious Disease

NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium
PT	Preferred Term
pUC ori	Plasmid origin of replication
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

16.0 REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020,**92**:401-402.
2. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O*, et al.* The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020,**91**:264-266.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y*, et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020,**395**:497-506.
4. GenBank. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. In; 2020.
5. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG*, et al.* Author Correction: A new coronavirus associated with human respiratory disease in China. *Nature* 2020,**580**:E7.
6. World Health Organization. Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance. In; 2020.
7. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report. In; 2020.
8. Centers for Disease Control and Prevention. First Travel-related Case of 2019 Novel Coronavirus Detected in United States. In; January 21, 2020.
9. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. In; 2020.
10. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. In; March 11, 2020.
11. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z*, et al.* SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020.
12. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
13. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol* 2020,**41**.
14. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly* 2020,**2**:113-122.
15. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J*, et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020,**395**:514-523.
16. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C*, et al.* Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med* 2020,**382**:970-971.
17. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J*, et al.* Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill* 2020,**25**.
18. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X*, et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020,**26**:672-675.
19. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020,**27**.
20. Centers for Disease Control and Prevention. Symptoms of Coronavirus. In; 2020.
21. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL*, et al.* Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med* 2020.

22. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. *BMJ* 2020,**369**:m1375.
23. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L*, et al.* Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003,**300**:1966-1970.
24. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL*, et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003,**361**:1767-1772.
25. Tsang TK, Cowling BJ, Fang VJ, Chan KH, Ip DK, Leung GM*, et al.* Influenza A Virus Shedding and Infectivity in Households. *J Infect Dis* 2015,**212**:1420-1428.
26. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L*, et al.* Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Front Immunol* 2020,**11**:827.
27. US FDA. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Remdesivir (Gs-5734™). In; 2020.
28. US FDA. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Chloroquine Phosphate Supplied From The Strategic National Stockpile For Treatment Of Covid-19 In Certain Hospitalized Patients. In; 2020.
29. 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**:2078-2088.
30. Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K*, et al.* Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019,**19**:1013-1022.
31. Suschak JJ, Williams JA, Schmaljohn CS. Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Hum Vaccin Immunother* 2017,**13**:2837-2848.
32. Manickan E, Karem KL, Rouse BT. DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology? *Crit Rev Immunol* 2017,**37**:483-498.
33. Porter KR, Raviprakash K. DNA Vaccine Delivery and Improved Immunogenicity. *Curr Issues Mol Biol* 2017,**22**:129-138.
34. Li L, Petrovsky N. Molecular mechanisms for enhanced DNA vaccine immunogenicity. *Expert Rev Vaccines* 2016,**15**:313-329.
35. Marc MA, Dominguez-Alvarez E, Gamazo C. Nucleic acid vaccination strategies against infectious diseases. *Expert Opin Drug Deliv* 2015,**12**:1851-1865.
36. Grunwald T, Ulbert S. Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases. *Clin Exp Vaccine Res* 2015,**4**:1-10.
37. Tregoning JS, Kinnear E. Using Plasmids as DNA Vaccines for Infectious Diseases. *Microbiol Spectr* 2014,**2**.
38. Williams JA. Improving DNA vaccine performance through vector design. *Curr Gene Ther* 2014,**14**:170-189.
39. Liu MA. DNA vaccines: an historical perspective and view to the future. *Immunol Rev* 2011,**239**:62-84.
40. Wahren B, Liu MA. DNA Vaccines: Recent Developments and the Future. *Vaccines (Basel)* 2014,**2**:785-796wahren.
41. Ledgerwood JE, Graham BS. DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases. *Hum Vaccin* 2009,**5**:623-626.

42. Keefer MC, Graham BS, Belshe RB, Schwartz D, Corey L, Bolognesi DP*, et al.* Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network. *AIDS Res Hum Retroviruses* 1994,**10**:1713-1723.
43. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S*, et al.* Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *Medrxiv Preprint* 2020.
44. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA*, et al.* A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol* 2006,**13**:1267-1277.
45. Prud'homme GJ, Glinka Y, Khan AS, Draghia-Akli R. Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases. *Curr Gene Ther* 2006,**6**:243-273.
46. Hirao LA, Wu L, Khan AS, Hokey DA, Yan J, Dai A*, et al.* Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques. *Vaccine* 2008,**26**:3112-3120.
47. Rosati M, Valentin A, Jalah R, Patel V, von Gegerfelt A, Bergamaschi C*, et al.* Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation. *Vaccine* 2008,**26**:5223-5229.
48. Curcio C, Khan AS, Amici A, Spadaro M, Quaglino E, Cavallo F*, et al.* DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice. *Cancer Gene Ther.* 2008,**15**:108-114.
49. Ugen KE, Kutzler MA, Marrero B, Westover J, Coppola D, Weiner DB*, et al.* Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation. *Cancer Gene Ther.* 2006,**13**:969-974.
50. 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.

17.0 APPENDICES

17.1 APPENDIX A: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIAL

Table for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Vital Signs[c]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C)[d] (°F)[d]	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40.0 102.1-104.0	> 40.0 > 104.0
Tachycardia - beats per minute	101-115	116-130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute[e]	50-54	45-49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141-150	151-155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91-95	96-100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85-89	80-84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17-20	21-25	> 25	Intubation

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
[c] Subject should be at rest for all vital sign measurements.
[d] Oral temperature; no recent hot or cold beverages or smoking.
[e] When resting heart rate is between 60-100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or < 400 gms/24 hours	4-5 loose stools or 400-800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

U.S. Department of Health and Human Services, Food and Drug Administration, and Center for Biologics Evaluation and Research. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical 2007 Sep; 3-5

17.2 APPENDIX B: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists adverse events of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
Other	Acute cardiac failure
	Acute kidney failure
	Septic shock-like syndrome

Signature Page for VV-TMF-00448 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 22-May-2020 16:03:32 GMT+0000

Signature Page for VV-TMF-00448 v1.0

COVID19-311

Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Adults at High Risk of SARS-CoV-2 Exposure

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 2.0

Protocol Version Date: 15-Jun-2020

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted]Jr., M.D., FACP, FIDSA
[redacted], [redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted]Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 1.0, dated 22May2020, to Version 2.0, dated 15Jun2020. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. The trial design has been modified as follows:
    a. The expected sample size of the trial has been increased to 6178 subjects. This is based on a revision of the lower bound of the two-sided 95% confidence interval for vaccine efficacy which has been increased from >15% to >30% in order to apply a more stringent criterion requiring the product to be more than modestly effective.
    b. The trial design has been modified to utilize a staggered approach to enrollment by initiating dosing in the 18-50 year old subjects and to expand enrollment to include subjects older than 50 years of age when safety and immunogenicity in this older age group has been confirmed using data due to be available from the ongoing COVID19-001 clinical trial.
        i. Additionally, minimum targets of 15% of the total sample size of subjects in the 51-64 age category and 5% of the total sample size of subjects in the 65 years and older category have been included. Stipulating a minimum enrollment of subjects 51 years of age or older will ensure that those who bear disproportionate risk for COVID-19 disease will contribute towards the primary endpoint.
    c. The enrollment of 100 seropositive subjects has been removed, as the likelihood of generating meaningful efficacy data from that group is low.
        i. Based on this modification, an exclusion criterion has been added to exclude subjects with positive SARS-CoV-2 test at Screening.
2. The endpoints for the trial have been revised as follows:
    a. The primary endpoint surveillance period has been extended from 6 months to 12 months post-dose 2. This will allow a longer surveillance period to detect COVID-19 disease cases that will contribute to the primary endpoint.
    b. Secondary endpoints with the surveillance time period starting 14 days post-dose 2 through 6 months post-dose 2 have been removed for consistency with the update to the primary endpoint surveillance period.
    c. A secondary endpoint of all-cause mortality has been added which will complement evaluation of COVID-19 disease-specific mortality.
    d. The secondary endpoint related to short term efficacy period has been removed as it is unlikely to observe an effect within the short timeframe specified in the endpoint.
    e. The definition of seroconversion in the secondary endpoint has been included as “at least fourfold rise over baseline”.
3. The eligibility criteria for the trial has been revised as follows:
    a. Additional description of the target study population has been included in the inclusion criteria to provide clarity related to enrollment of subjects “with high risk of exposure to SARS-CoV-2”. The revision to the inclusion criterion will provide clarity to the investigator regarding the types of subjects to be recruited.

b. We will no longer exclude subjects based on BMI given that vaccines will be administered intradermally and should not be influenced by BMI.

c. The exclusion criterion related to medical conditions has been modified to be more inclusive, to permit subjects who may be at greater risk for Severe COVID-19 disease due to their chronic medical conditions and thereby be more likely to benefit from an effective vaccine.

d. The exclusion criterion that includes a restriction of blood donation has been revised to include a restriction for receipt of a blood transfusion within 1 month prior to Day 0, which could be an indication of a medical concern that has not been identified within other criteria.

e. The exclusion criterion related to alcohol or substance abuse/dependence has been expanded to exclude current illicit drug use but allow for marijuana use.

4. The Schedule of Events has been revised as follows:

a. The number of in-person visits has been reduced in favor of phone call visits. This is intended to reduce the need for subjects to travel to the study site for frequent visits. The visit and phone call frequency has remained bi-weekly through Day 210 of the study and has been revised to approximately monthly after Day 210.

b. A COVID-19 convalescent visit has been added to the Schedule of Events with the intent of re-evaluating subjects approximately 28 days after symptom onset for subjects with virologically-confirmed COVID-19 infection during the trial.

c. Collection of safety labs (CBC with differential, Chemistry, routine urinalysis) post-screening will only be collected in a subset of subjects at selected sites given that that there is no requirement for safety laboratory testing for Phase 3 trials as per FDA and that there have been no safety concerns identified from earlier studies that would require extensive safety laboratory monitoring.

d. Collection of saliva samples for SAR-CoV-2 RT-PCR testing has been clarified to indicate that in-office collection time points for Screening, Day 0, Day 28, EOS and COVID-19 visits will be tested at the time of collection. All other saliva specimens will be stored frozen and will be selectively tested if a SARS-CoV-2 serology test becomes positive.

e. A subject diary has been added to collect temperature, solicited injection site reactions and solicited systemic adverse events for 7 days following each dose in a subset of subjects.

5. Preliminary safety data from the COVID19-001 study has been removed and a reference to the INO-4800 Investigator's Brochure has been added. The Investigator's Brochure is the standard location for safety and immunogenicity information related to Inovio products.

6. The case definitions have been revised as follows:

a. The case definition for virologically-confirmed COVID-19 disease has been updated within the protocol to align with the CDC definition.

b. Case definitions for non-severe and severe COVID-19 disease have been included to replace previous definitions for mild, moderate, severe and critical COVID-19 disease. The revised case definitions are aligned with CDC definitions.

c. The case definition for suspected COVID-19 disease has been removed as it is no longer needed for the protocol.

7. An Endpoint Adjudication Committee has been added for the purpose of adjudication of suspected COVID-19 cases in the trial and clarification has been made to the protocol that the adjudication of cases will not be performed by the DSMB.
8. The requirement to collect serial saliva samples every 2 days for 20 days in the event of acute SARS-CoV-2 infection has been removed as this collection did not support any of the study endpoints and may be too onerous on subjects when they are ill.
9. Instruction has been added regarding subjects taking their temperature daily at home starting on the Day 0 visit for the duration of the trial and contacting the site in the event of a fever higher than 100.4°F/38°C. This will aid in proactive identification of COVID-19 cases.
10. The text has been clarified to indicate that during assessment for suspected COVID-19 disease, the investigator may perform additional diagnostic testing to rule out other possible etiologies (e.g. influenza).
11. Additional procedures were added to help identify vaccine-enhanced disease. A stopping rule was added to reflect that the investigator should notify the Medical Monitor immediately in the event of any suspected Severe COVID-19 disease case(s). The sequential steps triggered by this notification are delineated to include the possible convening of the DSMB to evaluate the unblinded data for signals of vaccine-enhanced disease and render a recommendation whether to halt the trial.
12. Medical Monitor contact information was added to facilitate appropriate communication pathways for sites.
13. The funding source of the trial was clarified to indicate that Inovio Pharmaceuticals is the Sponsor and Department of Defense, Joint Program Executive Office is providing funding for the study.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 3

Estimated Number of Clinical Trial Centers and Countries/Regions: Up to 30 centers in the US

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 disease in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is a Phase 3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800 (1.0mg), administered by intradermal (ID) injection followed immediately by electroporation (EP) using CELLECTRA® 2000 device using a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objective of this trial is to evaluate the efficacy of INO-4800 in seronegative subjects.

Approximately 6178 seronegative subjects 18 years of age or older are expected to be enrolled and will be randomized at a 1:1 ratio to receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001). See Table 1. Enrollment at the start of the trial will be initiated in subjects 18-50 years of age. Following confirmation that the COVID19-001 Phase 1 trial's safety and immunogenicity data is acceptable in subjects older than 50 years of age, the trial will expand enrollment to include subjects older than 50 years of age. A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be 65 years of age and older.

Table 1: COVID19-311 Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	Total Dose
INO-4800	3089	0, 28	1	1.0 mg	2.0 mg
Placebo	3089	0, 28	1	0	0
Total	6178				

The trial is case-driven. Among seronegative subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6178 seronegative subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The sample size may be increased if the underlying attack rate is lower than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2.

All subjects, investigating site staff (excluding site pharmacy staff) and the Sponsor will be blinded throughout the trial. A group-level unblinding will occur when all subjects' data is complete for the primary efficacy timeframe.

A Data Safety Monitoring Board (DSMB) will convene regularly throughout the trial to review unblinded safety data. An independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases. Details of each committee's scope will be provided in charters.

Criteria for Evaluation:

Research Hypothesis:
INO-4800 delivered ID followed by EP using CELLECTRA® 2000 will provide protection against virologically-confirmed COVID-19 in subjects at high risk of SARS-CoV-2 exposure.

Primary Objective	**Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))
Secondary Objectives	**Associated Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the timing of symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease

5. Evaluate the binding antibody response to INO-4800	5a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody titers 5b. Incidence of seroconversion (at least fourfold rise over baseline) by SARS-CoV-2 Spike glycoprotein antigen specific binding antibody assay
Exploratory Objective	**Associated Exploratory Endpoint**
1. Evaluate the expanded immunological profile by assessing both neutralizing antibody response and T cell immune responses	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by live virus neutralizing or pseudovirus assays

Efficacy Assessment:

Subjects will receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive virologic test result confirmation will be reviewed by the EAC.

Safety Assessment:

Subjects will be followed for safety during the entire duration of trial participation through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. Solicited local and systemic AEs will be collected for 7 days following each dose. SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization.

Please refer to the Schedule of Events (Table 2) for safety assessments to be performed.

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 2*).* Assays such as Binding ELISA, neutralizing antibody, and ELISpot will be evaluated at serial timepoints.

Clinical Trial Population:

Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years or older.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, physical examination and vital signs performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used:
    1. Retail/service workers (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers,

Transportation Security Administration screening staff, and elementary school teachers)
2. Factory workers (when working in confined settings with large numbers of employees)
3. Nursing home staff or correctional facility staff
4. First responders (emergency medical technicians, police who are regularly assigned on patrol)
5. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists but not necessarily physicians unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
6. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
g. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening (subjects who are positive for Hepatitis C antibody but are in remission as defined by undetectable HCV RNA level ≥ 12 weeks after completion of HCV therapy may be enrolled)
h. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0;

f. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS; documented receipt of placebo in previous trial would be permissible for trial eligibility.
g. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies;
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of 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);
    - History of solid organ or bone marrow transplantation;
    - History of receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
    - Any metal implants or implantable medical device within the electroporation site;
j. Blood donation or transfusion within 1 month prior to Day 0;
k. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
l. Reported ongoing smoking or vaping;
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment: Investigational Product: A single 1.0mg ID injection of INO-4800 (~0.1mL dose volume) followed immediately by EP administered at Day 0 and Day 28 (±3 days) Placebo: A single ID injection of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered at Day 0 and Day 28 (±3 days)
Formulation: INO-4800 is formulated in sodium chloride and sodium citrate (SSC) buffer, refrigerated.

TABLE 2 - SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 8	Tel #3-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 56 (±5d)	Phone call - Days 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[n]	COVID-19 convalescent visit[o]
		Pre	Post		Pre	Post												
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical history	X	X																
Demographics	X																	
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X		X		X		X	X	X
Vital Signs	X	X			X			X		X		X		X		X	X	X
Height and Weight	X																	
CBC with differential	X	X[p]			X[p]			X[p]								X	X	
Chemistry[c]	X	X[p]			X[p]			X[p]								X	X	
HIV, HBV, HCV Serology	X																	
Urinalysis Routine[d]	X	X[p]			X[p]			X[p]								X	X	
Pregnancy Test[e]	X	X			X											X		
INO-4800 or Placebo + EP[f]		X			X													
Download EP Data[g]			X			X												
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X			X			X		X		X				X		X
Humoral Samples[j]		X			X			X		X		X				X		X
SARS-CoV-2 Serology[k]	X	X			X			X		X		X		X		X	X	X
SARS-CoV-2 RT-PCR (Saliva)[l]	X	X			X			X	X	X	X	X	X	X	X	X	X[m]	X[m]
Distribute Diary[p]			X			X												
Review/Collect Diary[p,q]				X	X		X	X										

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at screening and Day 393 (or EOS). Targeted physical exam at all other visits.
c. Includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin, and hemoglobin A1c (hemoglobin A1c collected at screening only).

d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at screening. Urine pregnancy test at other visits.
f. An intradermal injection in skin preferably over deltiod muscle followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. Cellular responses utilizing ELIspot assay requires 34 mL of whole blood; collect 8.5 mL of whole blood in each of four 10 mL Acid Citrate Dextrose (ACD, Yellow top) tubes per time point. Note: Collect a total of 68 mL whole blood on Day 0 prior to 1st dose.
j. Humoral responses utilizing the S-Binding ELISA, NP-Binding ELISA and SARS-CoV-2 neutralization assays require a total of 8.5 mL of serum collected in a 10-mL red top serum collection tube per time point. Note: Collect four aliquots of 1 mL each (total 4 mL) prior to dosing on Day 0 and at each time point.
k. SARS-CoV-2 antibody.
l. Saliva will be collected at study visits and bi-weekly at home between office visits. In-office collection time points for Screening, Day 0, Day 28, EOS and COVID-19 visits will be tested at the time of collection. All other saliva specimens will be stored frozen and will be selectively tested if a SARS-CoV-2 serology test becomes positive. The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.
m. Nasopharyngeal, oropharyngeal swabs and saliva specimens.
n. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The virologic confirmation of a case will be based on SARS-CoV-2 RT-PCR. Additional safety testing will be collected to understand the impact on various organ systems. Additional diagnostic testing (e.g., influenza diagnostics) may be ordered at the discretion of the Investigator.
o. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test.
p. Implemented in approximately 500 subjects from selected sites.
q. Diary should be reviewed at the 7 day post-dose phone call and collected at the next in-office visit.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to US and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

The lack of available therapy in conjunction with increasing numbers of global cases indicate that SARS-CoV-2 infection remains a serious unmet medical concern. Appropriate measures to prevent, control and treat existing and future infections are in dire need.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [1-3]. These cases were announced on January 6, 2020 as testing negative for influenza, SARS, and MERS. On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named “Wuhan-Hu-1.” The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [4, 5]. That gene sequence was publically posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [6, 7], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, “COVID-19,” associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The cluster of human cases first identified pneumonia of unknown origin infections was comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting an animal as the source of the novel virus transmission to humans.

The first U.S. case of COVID-19 was detected in Washington State, confirmed on and as announced January 21, 2020 by the Washington State Department of Health and the U.S. Centers for Disease Control and Prevention (US CDC) [8]. That was a case of a traveler who had returned from Wuhan, China. Since that case detection, human-to-human local transmission began (or continued from previously undetected infections) in the U.S., and as of May 17, 2020, nearly 1.5 million lab-confirmed US COVID-19 cases and nearly 90,000 US deaths due to COVID-19 have been reported [9]. COVID-19 cases have been reported from all 50 states and several territories.

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) infectious agents in a growing number of coronaviruses which have evolved to infect humans. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and then progressed to be declared on March 11, 2020 as a pandemic [10], associated with substantial morbidity and mortality [11]. The pandemic of COVID-19 includes scope of lab-confirmed cases reported by virtually all countries and COVID-19 deaths reported by many of those countries. As of May 17, 2020, a total of over 4.7 million lab-confirmed COVID-19 cases have been reported internationally, including nearly 315,000 deaths [9]. However, and very importantly,

because this is from a new pathogen and thus lab testing and reporting are not widely available and thus incomplete, the true number of cases of COVID-19 is likely far higher than reported, and the true number of SARS-CoV-2 infections – regardless of disease – is thought to be many (perhaps dozens of) times the number of detected infections and reported COVID-19 cases.

An article in *JAMA* by Wu and McGoogan [12] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [13]. That report found that among a total of 72,314 case records, 44,672 were classified as confirmed cases of SARS-CoV-2 infection (62%; diagnosis based on positive viral nucleic acid test result on throat swab samples), 16,186 as suspected cases (22%; diagnosis based on symptoms and exposures only, no test was performed because testing capacity was insufficient to meet current needs), 10,567 as clinically diagnosed cases (15%; this designation is being used in Hubei Province only; in these cases, no test was performed but diagnosis was made based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia), and 889 as asymptomatic cases (1%; diagnosis by positive viral nucleic acid test result but lacking typical symptoms including fever, dry cough, and fatigue) [14]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [14]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Because of the novelty of SARS-CoV, the COVID-19 it causes and the serious outcomes in some patients, and the speed of propagation worldwide, unsurprisingly there has been an explosion of epidemiological, clinical, virological, and other data have emerged from China, the United States, and many other countries about this new virus and disease. These data in summary have further established that 1) SARS-CoV-2 is transmitted person-to-person [15], even from those asymptomatic or presymptomatic [16-18], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.5 to 6.49, with a mean average of 3.28 and a median average of 2.79 [19], 3) the constellation of symptoms, signs, and an incubation period range of 2 to 14 days [20], and 4) the asymptomatic proportion of those infected being substantial, perhaps 50% or even up to 80% [15, 21, 22]. Further, research has found that the risk of death from COVID-19 increases with age and for those with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned case-fatality ratio and similar estimates are from crude analyses that have only or largely been of moderate to serious cases and not included minor cases that did not present to health care. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [3] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5 12%) and secondary infection (n=4, 10%).

Transmission of SARS-CoV-2 occurred mainly after days of illness [23] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [24]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [25] and appears different from that seen in patients infected with SARS-CoV [24]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [18].

T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of the counts of total T cells, and $CD4^+$and $CD8^+$ T cell subsets, as well as serum cytokine concentration based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection, admitted into two hospitals in Wuhan from December 2019 to January 2020, and 40 healthy controls in the same two hospitals receiving routine physical examination. The number of total T cells, and $CD4^+$ and $CD8^+$ T cells were dramatically reduced in COVID-19 infected patients, especially among elderly patients (≥60 years of age) and in patients requiring Intensive Care Unit (ICU) care. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells lower than 800/μL, 300/μL, or 400/μL, respectively, are negatively correlated with patient survival [26].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Hospitals can provide supportive care for infected people. Currently, no licensed preventative vaccine or anti-viral therapy is available as indicated for SARS-CoV-2 infection or COVID-19, except for Emergency Use Authorization (EUA). Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated. Remdesivir has received Emergency Use Authorization for treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease [27]. Chloroquine Phosphate also has received EUA for treatment of adults and adolescents who are hospitalized with COVID-19 for whom a clinical trial is not available [28]. Hydyroxychloroquine, with and without azithromycin, is being investigated in multiple clinical trials, as is plasma-derived polyclonal antibodies and immune globulin, among other therapies.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. No specific treatment for COVID-19 is currently available, thus highlighting the need for effective therapeutic and preventive solutions. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat existing and future infections.

To address this critical need for a medical countermeasure for prevention of further dissemination of SARS-CoV-2, we have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and the possibility of leveraging established regulatory pathways to the clinic. Furthermore, this technology has demonstrated proof of concept efficacy and safety in humans in a phase 2b randomized, double-blind, placebo-controlled study [29], for human papillomavirus (HPV) associated cervical pre-cancer and is currently in two multinational phase 3 trials for that indication (NCT03185013 and NCT03721978) and several phase 2 trials for related and other indications. For the development of a SARS-COV-2 vaccine candidate, we have built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine. In a phase 1 clinical study, the MERS-CoV coronavirus vaccine was well tolerated and immune response was induced in more than 85% of participants after two vaccinations, and durable through 1 year of follow-up [30].

1.3.1 DOSE AND REGIMEN RATIONALE

The intended use for INO-4800 is for both routine prophylaxis and use during an outbreak situation. As such, there is a desire to demonstrate the ability of the vaccine to drive immune responses within 4-8 weeks of administration, which supports evaluation of a dose regimen that includes Day 0 and Day 28.

In this study, 1.0 mg of vaccine is administered by ID injection and followed by EP at Day 0 and Day 28. The dose selection is supported by the well tolerated safety profile in the phase 1 trial of INO-4800 (COVID19-001, NCT04336410) as well as our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17].

Safety data for INO-4800 is provided in the Investigator's Brochure.

1.3.2 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [31-40]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, Middle East Respiratory Syndrome (MERS) coronavirus, rabies virus, Severe Acute Respiratory Syndrome (SARS) coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as

plasmodium, mycoplasma, and many more [39, 41]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [42]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [43].

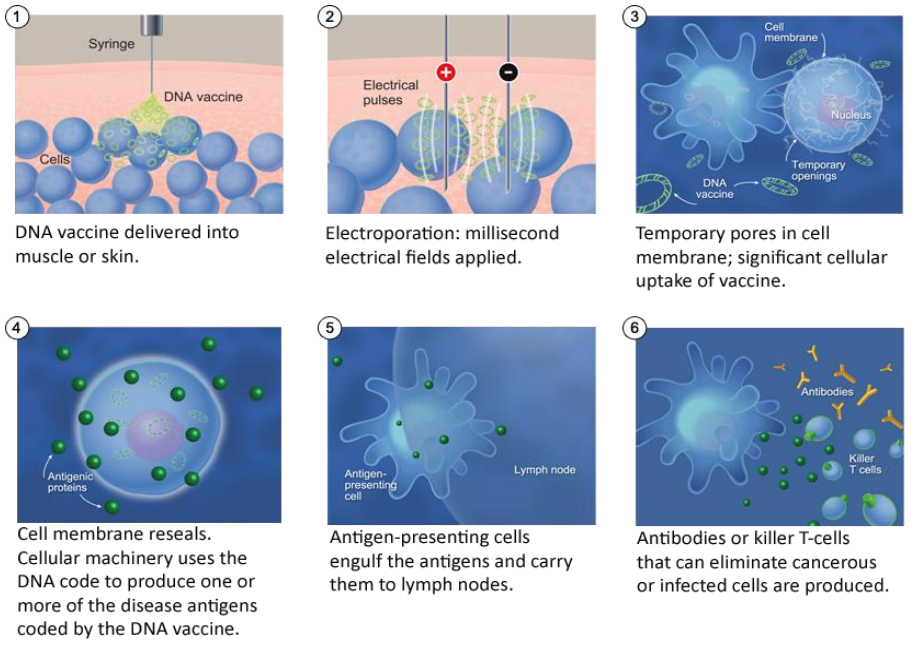
Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [44]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.3 USE OF ELECTROPORATION WITH DNA VACCINES

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 1). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [45]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens [45] for the activation of both cellular and humoral responses [46, 47]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [47]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [48, 49].

The Inovio Pharmaceuticals' constant current EP device [45] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device will be used in this clinical trial. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [50].

Figure 1: How Electroporation Works in the Body



1.4 POTENTIAL BENEFITS AND RISKS

No specific AE has been identified as a risk. There may be potential benefit for prevention of COVID-19 disease, but efficacy is still unknown. Data gathered in this trial will be useful for future development of this prophylactic vaccine against SARS-CoV-2 infection.

Additional details regarding the benefits and risks for subjects participating in this clinical trial may be found in the Investigator's Brochure (IB).

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety and efficacy of INO-4800 for future development.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP using CELLECTRA® 2000 will provide protection against virologically-confirmed COVID-19 in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is a Phase 3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800 (1.0mg), administered by intradermal (ID) injection followed immediately by electroporation (EP) using CELLECTRA® 2000 device using a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objective of this trial is to evaluate the efficacy of INO-4800 in seronegative subjects.

Approximately 6178 seronegative subjects 18 years of age or older are expected to be enrolled and will be randomized at a 1:1 ratio to receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001). See Table 1. Enrollment at the start of the trial will be initiated in subjects 18-50 years of age. Following confirmation that the COVID19-001 Phase 1 trial's safety and immunogenicity data is acceptable in subjects older than 50 years of age, the trial will expand enrollment to include subjects older than 50 years of age. A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be 65 years of age and older.

The trial is case-driven. Among the 6178 subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6178 seronegative subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The sample size may be increased if the underlying attack rate is lower than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2.

All subjects, investigating site staff (excluding site pharmacy staff) and the Sponsor will be blinded throughout the trial. A group-level unblinding will occur when all subjects' data is complete for the primary efficacy timeframe.

A Data Safety Monitoring Board (DSMB) will convene regularly throughout the trial to review unblinded safety data. An independent, blinded EAC will review and confirm COVID-19 cases. Details of each committee's scope will be provided in charters.

3.1 PRIMARY OBJECTIVES

See Table 3.

3.2 PRIMARY ENDPOINTS

Table 3: Primary Objective and Associated Endpoints

Primary Objective	Associated Primary Endpoint
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))

3.3 SECONDARY OBJECTIVES

See Table 4.

3.4 SECONDARY ENDPOINTS

Table 4: Secondary Objectives and Associated Endpoints

Secondary Objectives	Associated Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the timing of symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease.
5. Evaluate the binding antibody response to INO-4800	5a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody titers 5b. Incidence of seroconversion (at least fourfold rise over baseline) by SARS-CoV-2 Spike glycoprotein antigen specific binding antibody assay

3.5 EXPLORATORY OBJECTIVE

See Table 5.

3.6 EXPLORATORY ENDPOINT

Table 5: Exploratory Objectives and Associated Endpoints

Exploratory Objective	Associated Exploratory Endpoints
1. Evaluate the expanded immunological profile by assessing both neutralizing antibody response and T cell immune responses	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot. 1b. Neutralizing antibody response measured by live virus neutralizing or pseudovirus assays

3.7 EFFICACY ASSESSMENT

Subjects will receive either investigational product (1.0mg INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive virologic test result will be reviewed by the independent blinded EAC. The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

• Positive testing by RT-PCR assay (any source) with any of the following COVID-19 related symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

3.7.1.1 Case Definition for Non-Severe COVID-19

• Confirmed COVID-19 disease (per Section 3.7.1);

• Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.2).

3.7.1.2 Case Definition for Severe COVID-19

• Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
d. Significant acute renal, hepatic, or neurologic dysfunction,
e. Admission to an ICU, or
f. Death.

3.7.2 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED SARS-COV-2 INFECTION

• Positive testing by RT-PCR assay (any source);

• Irrespective of clinical signs and symptoms.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the entire duration of trial participation through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. Solicited local and systemic AEs will be collected for 7 days following each dose. SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization.

Please refer to the Schedule of Events (Table 2) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 2*)*. Assays such as Binding ELISA, neutralizing antibody, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, physical examination and vital signs performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used:
    1. Retail/service workers (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, and elementary school teachers)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Nursing home staff or correctional facility staff
    4. First responders (emergency medical technicians, police who are regularly assigned on patrol)
    5. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists but not necessarily physicians unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
    6. Others, if approved by the medical monitor;
f. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
g. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening (subjects who are positive for Hepatitis C antibody but are in remission as defined by undetectable HCV RNA level ≥ 12 weeks after completion of HCV therapy may be enrolled)
h. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        - hormonal contraception including implants, injections or oral;

- two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
- abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0;
f. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS; documented receipt of placebo in previous trial would be permissible for trial eligibility.
g. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
h. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies;
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
   - Current or anticipated use of 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);
   - History of solid organ or bone marrow transplantation;
   - History of receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
l. Reported ongoing smoking or vaping;
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 2) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Sterile saline sodium citrate (SSC) buffer (SSC-0001), which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps, will be used as the placebo.

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 vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering current controlled electrical pulses as follows:

- An EP treatment consists of four pulses.
- An Array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue.
- Voltage levels are limited to 200 volts (V) for patient safety.

- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device for ID administration is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles.

5.2 DOSING REGIMENS

- Investigational Product: A single 1.0mg ID injection of INO-4800 (~0.1mL dose volume) followed immediately by EP administered at Day 0 and Day 28 (±3 days)
- Placebo: A single ID injection of SSC-0001 (~0.1mL) followed immediately by EP administered at Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is double-blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel will be blinded throughout the trial. There is no difference in appearance for both the INO-4800 product and the placebo; however, they are packaged in different sized vials. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

The PI may request to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is essential for proper clinical management of the subject, as judged by the PI. It is preferred, but not required, that the PI first contact the Medical Monitor (MM) to discuss options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the Investigator's Brochure (IB).

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, it must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a participant is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

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

The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training from Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigative site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Table 2) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed within 30 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 30 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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics and document any ongoing, pre-existing conditions;
- Collect adverse events (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect serum for HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C serology (Section 6.4) per national guidelines;
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or occurred within the 12 weeks prior to Screening. 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. Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (investigational product or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (will be implemented in approximately 500 subjects from selected sites) (Section 6.4);
- Collect urine for routine urinalysis (will be implemented in approximately 500 subjects from selected sites) (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Review restrictions for injection and EP (Section 6.4.8);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new adverse events (Section 6.4.4);
- Download EP Data (Section 6.4.1.1);
- Distribute diaries and provide supplies for subject to use at home, as required (e.g. thermometer, wound guide).

6.1.2.2 Day 7 and Day 35 phone calls (post-dose phone calls)

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Review diary (Section 6.4).

6.1.2.3 Day 56 Visit

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (will be implemented in approximately 500 subjects from selected sites) (Section 6.4);
- Collect urine for routine urinalysis (will be implemented in approximately 500 subjects from selected sites) (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR and store in freezer (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.4 Phone calls (Days 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378)

Phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393. Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.10);
- Record current concomitant medications/treatments (Section 6.4.7);
- Remind subject to self-collect saliva sample and store in freezer (Section 6.4.9).

6.1.2.5 Days 126, 210 and 294 Visits

The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR and store in freezer; (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (except Day 294 visit) (Section 6.4.6);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.6 Day 393 Visit or EOS

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test (Section 6.4);
- Collect blood for CBC with differential and serum chemistry(Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (will be tested at the time of collection) (Section 6.4.9);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

6.1.2.7 COVID-19 Assessment Visit

Subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR. Additional safety testing will be collected to understand the impact on various organ systems. Additional diagnostic testing (e.g., influenza diagnostics) may be ordered at the discretion of the Investigator. The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect nasopharyngeal, oropharyngeal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

6.1.2.8 COVID-19 Convalescent Visit

For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect nasopharyngeal, oropharyngeal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects
- Explain the clinical trial
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description
  - Eligibility criteria for entering the clinical trial
  - Clinical trial treatments and follow-up procedures description
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives
    - Potential benefits and risks
    - Discomforts/inconveniences
    - Subject's rights and responsibilities

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30 day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a four digit site code and a three digit subject number starting with 001. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the Case Report Form (CRF).

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Table 2).

HEIGHT AND WEIGHT

Weight (kg) and height (cm) will be collected at Screening.

LABORATORY EVALUATIONS

At Screening and at visits specified in the Schedule of Events (Table 2), blood samples will be collected for safety assessments. Approximately 375-450 mL of blood will be drawn from each subject over the course of the study. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 at visits specified in the Schedule of Events (Table 2).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, BUN (blood urea nitrogen), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, total bilirubin (TBili), and hemoglobin A1c at Screening and at visits specified in the Schedule of Events (Table 2). Hemoglobin A1c will only be performed at Screening.

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and at visits specified in the Schedule of Events (Table 2). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

Antibodies to Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and HIV antibody or rapid test will be measured at Screening only. Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Table 2).

Pregnancy Testing:

For women of child bearing potential (WOCBP), a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit. 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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy.

DIARY

Diaries will be implemented in approximately 500 subjects from selected sites. Subjects will be provided a diary to record the following solicited local and systemic adverse events:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic systems
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary will be reviewed with the subject by the study staff during the phone calls on Day 7 and Day 35. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms

(pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be collected.

Any diary entry determined to meet the CTCAE criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the CTCAE guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INJECTION AND EP

Subjects will receive a two-dose regimen of INO-4800 or placebo by ID injection in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28.

Only if the deltoid area is not a suitable location (see exclusion criterion 'i'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

Blood will be drawn for serum chemistry and hematology and urinalysis will be performed at the visits listed in the Schedule of Events (Table 2) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued in September 2007 (Appendix A). Laboratory values that are not clinically significant (NCS) in the Investigator's opinion will not be reported as adverse events.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

Subjects will be queried regarding the occurrence of any adverse events including adverse events related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All adverse events will be captured from the time of the informed consent until 28 days post-dose 2. Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

The IP administration procedure consists of an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of the electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug. Consequently, reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 6 below) and use the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (Appendix A). Administration (injection) site reactions and administration site pain will be evaluated starting 30 minutes following injection/EP. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 6: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

September 2007 "FDA Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Table 2) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Baseline (Day 0) immunology samples are required to

enable all immunology testing. Therefore a total of 68mL whole blood and 4mL serum is required prior to 1st dose. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

The additional immune responses to INO-4800 will be measured using assays that include neutralization, flow cytometry and ELIspot. Determination of additional analysis using assays not specified, such as assessment of immunological gene expression, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

6.4.7 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) must be recorded on 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.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor.

The decision to administer a prohibited medication/treatment (Section 6.4.8) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.8 RESTRICTIONS

Subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature >38.0 degrees Celsius or 100.4 degrees Fahrenheit) within 72 hours prior to each dosing.

Subjects should refrain from donating blood from Screening visit through the duration of the trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.9 SARS-CoV-2 TESTING

Serology SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 2: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on saliva specimens collected at Screening, Day 0, Day 28 and Day 393 or EOS visit. During other in-office study visits (see Table 2: Schedule of Events), saliva samples will be collected and stored frozen on

site. Bi-weekly home self-collections will be done by subjects, when possible, between study visits and stored frozen at the subject's home. The subject will be encouraged to document any symptoms present at the time of saliva collection and report them to the site. Testing may be selectively performed on the frozen saliva samples if the subject's SARS-CoV-2 serology test becomes positive.

The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.

If either the SARS-CoV-2 antibody or RT-PCR test result is positive during the trial, the subject will be notified of the result and will be requested to come to the clinic for an evaluation. During that visit, a blood sample will be collected for serologic testing and 3 specimens (nasopharyngeal swab, oropharyngeal swab and saliva) will be collected to detect SARS-CoV-2 using the RT-PCR assay.

6.4.10 COVID-19 DISEASE MONITORING

All subjects will be monitored through regularly scheduled clinic visits and phone calls for the development of symptoms suggestive of COVID-19 disease. Subjects should be instructed to take their temperature daily at home starting on the Day 0 visit for the duration of the trial and contact the site in the event of a fever higher than 100.4°F/38°C. Site personnel will arrange for a clinic visit for subjects reporting symptoms suggestive of COVID-19 (e.g., fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) at any time during the study. During that visit, a blood sample will be collected for serologic testing and 3 specimens (nasopharyngeal swab, oropharyngeal swab and saliva) will be collected to detect SARS-CoV-2 using the RT-PCR assay, and additional diagnostic testing (e.g., influenza diagnostics) may be ordered at the discretion of the Investigator. All suspected COVID-19 disease cases should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness.

If the specimen(s) are RT-PCR negative, the RT-PCR assay may be repeated if other possible etiologies such as influenza have been ruled out and a diagnosis of COVID-19 remains a possible diagnosis. Furthermore, SARS-CoV-2 RT-PCR detection may be performed on sputum, endotracheal aspirate, bronchoalveolar lavage samples or rectal samples, if available. Pulmonary CT scan findings showing typical interstitial pneumonia including ground-glass opacities may corroborate the diagnosis of COVID-19 disease. The formal radiologist's interpretation of the CT scan should be included as a source document.

Subjects with a confirmed COVID-19 diagnosis prior to dose 2 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, approximately 28 days after the date the positive SARS-CoV-2 sample was collected. Recovery from COVID-19 disease requires resolution of clinical symptoms and follow up testing according to Institutional policy.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued September 2007 (Appendix A).

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 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 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)

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
- 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
- Confirmed COVID-19 disease

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.
- Confirmed COVID-19 disease that requires hospitalization is recorded as an endpoint, and not recorded as an SAE.
- COVID-19 disease with an outcome of death is recorded as an endpoint, and not recorded as an SAE.
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event.
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF.

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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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, preferred term, severity and causal relationship to clinical trial treatment
- Changes in laboratory parameters
- Local and systemic injection site review; special attention will be paid to the examination of the injection site

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix B are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

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 further administration of the investigational product in the clinical trial
- 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment.
- Any Grade 4 adverse events related to study treatment.
- Any report of anaphylaxis related to study treatment.

- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 7: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 8: Medical Monitor Direct contact Information

Primary point of contact, ICON Medical Monitor: [redacted] M.D.
Email: [redacted]
Cell Phone: [redacted]
Inovio Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs and AESIs must be followed by the PI until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 number (SID)
- Investigational product(s) (IP) and/or study device
- Investigator causal relationship to the IP(s) and/or study 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 SAE 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 previous signs and/or symptoms will be subsumed 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 Toxicity Grading Scale for Healthy Adult and Adolescent

Volunteers Enrolled in Preventive Vaccine Clinical Trials (Food and Drug Administration [FDA] Guidance for Industry) (Appendix A).

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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

All suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition, by the EAC.

If the COVID-19 disease case reported is later determined not to be a confirmed case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following notification of the determination by the EAC.

If the COVID-19 disease case reported is later determined not to be a confirmed case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following notification of the determination by the EAC.

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose 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 dose administrations, 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. 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 a Pregnancy Information Collection Consent Form 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 two-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, infection, and timing of symptom resolution. Other secondary analyses concern safety and binding antibody response. Exploratory analyses concern cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq .70/(.70+k)$ *vs*. H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects with disease occurring prior to 14 days post-dose 2 will be excluded from the PP population. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population will be primary for the analysis of efficacy in this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analysis of efficacy.

The intention 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 considered supportive for the corresponding PP population for the analysis of efficacy.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY EFFICACY ANALYSIS

The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.705/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI for efficacy exceeds 30%.

For calculating k, an individual subject's follow-up time is either:

a) the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or

b) the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters (t, $p=\lambda v/(\lambda v+\lambda c)$). The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The secondary efficacy endpoint regarding timing of symptom resolution will be analyzed with Kaplan-Meier plots by treatment group.

8.5.2.2 Immunogenicity

Post-baseline antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean titers and associated 95% CIs.

Post-baseline seroconversion from ELISA will be compared between treatment groups using differences in proportions and associated Miettinen and Nurminen 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for immunogenicity analyses.

8.5.3 SAFETY ANALYSES

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will also be performed on the subset who are assigned to complete the 7-day post-dose diary. 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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations.

8.5.5.2 Medical History

The percentage of subjects with abnormal medical history findings will be summarized by body system, by treatment arm, for the ITT and PP populations.

8.5.5.3 Prior Medications

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 by treatment arm, for the ITT and PP populations.

8.5.6 INTERIM ANALYSES

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

8.5.7 MULTIPLICITY

Not applicable; there is one hypothesis that will be tested.

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Immunogenicity

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using a difference in medians and associated non-parametric 95% CIs.

Post-baseline decreases from baseline in neutralizing antibody response magnitudes will be compared between treatment groups using a difference in medians and associated non-parametric 95% Cis.

The summaries listed above will be stratified according to disease status of the subjects.
Valid samples for statistical analysis purposes will be those collected within the days of the specified visit according to the Schedule of Events. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.1 Concomitant Medications

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 by treatment arm, for the ITT and PP populations.

8.6 SAMPLE SIZE/POWER

The trial is case-driven. A total of 160 observed cases will be required to provide 90% power to declare the vaccine efficacious (>30%), utilizing the methodology described in Section 8.5.1 and assuming a true efficacy of 60%. A sample size of 6178 subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Subjects will be randomized (1 INO-4800:1 Placebo).

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of participants to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

- Submit continuing review reports to the IRB/REB/EC as required, and request re-review and approval of the clinical trial at least once a year during the conduct of the clinical trial
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects
- Notify the IRB/REB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events
- Obtain approval from the IRB/REB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required
- Submit reports on, and reviews of, the clinical trial and its progress to the IRB/REB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines
- Maintain a file of clinical trial-related information (refer to clinical trial files) that includes all correspondence with the IRB/REB/EC

- Notify the IRB/REB/EC when the clinical trial is completed (i.e., after the last clinical trial visit of the final clinical trial subject)
- After clinical trial completion (within three [3] months is recommended), provide the IRB/REB/EC with a final report on the clinical trial

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately.

Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will meet approximately once per month, at a minimum. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
  - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
  - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and Department of Defense, Joint Program Executive Office is providing funding for the study. Clinical trial insurance has been taken out according to 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 per 21 CFR Part 54.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bGH polyA	Bovine growth hormone 3' end poly-adenylation signal
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCO_3	Biocarbonate
hCMV	Human CMV
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
K	Potassium
KanR	Kanamycin resistance gene
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NIAID	National Institute for Allergy and Infectious Disease

NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium
PT	Preferred Term
pUC ori	Plasmid origin of replication
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

16.0 REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020,**92**:401-402.
2. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O*, et al.* The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020,**91**:264-266.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y*, et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020,**395**:497-506.
4. GenBank. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. In; 2020.
5. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG*, et al.* Author Correction: A new coronavirus associated with human respiratory disease in China. *Nature* 2020,**580**:E7.
6. World Health Organization. Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance. In; 2020.
7. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report. In; 2020.
8. Centers for Disease Control and Prevention. First Travel-related Case of 2019 Novel Coronavirus Detected in United States. In; January 21, 2020.
9. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. In; 2020.
10. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. In; March 11, 2020.
11. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z*, et al.* SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020.
12. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
13. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol* 2020,**41**.
14. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly* 2020,**2**:113-122.
15. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J*, et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020,**395**:514-523.
16. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C*, et al.* Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med* 2020,**382**:970-971.
17. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J*, et al.* Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill* 2020,**25**.
18. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X*, et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020,**26**:672-675.
19. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020,**27**.
20. Centers for Disease Control and Prevention. Symptoms of Coronavirus. In; 2020.
21. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL*, et al.* Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med* 2020.

22. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. *BMJ* 2020,**369**:m1375.
23. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L*, et al.* Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003,**300**:1966-1970.
24. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL*, et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003,**361**:1767-1772.
25. Tsang TK, Cowling BJ, Fang VJ, Chan KH, Ip DK, Leung GM*, et al.* Influenza A Virus Shedding and Infectivity in Households. *J Infect Dis* 2015,**212**:1420-1428.
26. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L*, et al.* Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Front Immunol* 2020,**11**:827.
27. US FDA. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Remdesivir (Gs-5734™). In; 2020.
28. US FDA. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Chloroquine Phosphate Supplied From The Strategic National Stockpile For Treatment Of Covid-19 In Certain Hospitalized Patients. In; 2020.
29. 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**:2078-2088.
30. Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K*, et al.* Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019,**19**:1013-1022.
31. Suschak JJ, Williams JA, Schmaljohn CS. Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Hum Vaccin Immunother* 2017,**13**:2837-2848.
32. Manickan E, Karem KL, Rouse BT. DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology? *Crit Rev Immunol* 2017,**37**:483-498.
33. Porter KR, Raviprakash K. DNA Vaccine Delivery and Improved Immunogenicity. *Curr Issues Mol Biol* 2017,**22**:129-138.
34. Li L, Petrovsky N. Molecular mechanisms for enhanced DNA vaccine immunogenicity. *Expert Rev Vaccines* 2016,**15**:313-329.
35. Marc MA, Dominguez-Alvarez E, Gamazo C. Nucleic acid vaccination strategies against infectious diseases. *Expert Opin Drug Deliv* 2015,**12**:1851-1865.
36. Grunwald T, Ulbert S. Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases. *Clin Exp Vaccine Res* 2015,**4**:1-10.
37. Tregoning JS, Kinnear E. Using Plasmids as DNA Vaccines for Infectious Diseases. *Microbiol Spectr* 2014,**2**.
38. Williams JA. Improving DNA vaccine performance through vector design. *Curr Gene Ther* 2014,**14**:170-189.
39. Liu MA. DNA vaccines: an historical perspective and view to the future. *Immunol Rev* 2011,**239**:62-84.
40. Wahren B, Liu MA. DNA Vaccines: Recent Developments and the Future. *Vaccines (Basel)* 2014,**2**:785-796wahren.
41. Ledgerwood JE, Graham BS. DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases. *Hum Vaccin* 2009,**5**:623-626.

42. Keefer MC, Graham BS, Belshe RB, Schwartz D, Corey L, Bolognesi DP*, et al.* Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network. *AIDS Res Hum Retroviruses* 1994,**10**:1713-1723.
43. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S*, et al.* Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *Medrxiv Preprint* 2020.
44. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA*, et al.* A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol* 2006,**13**:1267-1277.
45. Prud'homme GJ, Glinka Y, Khan AS, Draghia-Akli R. Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases. *Curr Gene Ther* 2006,**6**:243-273.
46. Hirao LA, Wu L, Khan AS, Hokey DA, Yan J, Dai A*, et al.* Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques. *Vaccine* 2008,**26**:3112-3120.
47. Rosati M, Valentin A, Jalah R, Patel V, von Gegerfelt A, Bergamaschi C*, et al.* Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation. *Vaccine* 2008,**26**:5223-5229.
48. Curcio C, Khan AS, Amici A, Spadaro M, Quaglino E, Cavallo F*, et al.* DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice. *Cancer Gene Ther.* 2008,**15**:108-114.
49. Ugen KE, Kutzler MA, Marrero B, Westover J, Coppola D, Weiner DB*, et al.* Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation. *Cancer Gene Ther.* 2006,**13**:969-974.
50. 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.

17.0 APPENDICES

17.1 APPENDIX A: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIAL

Table for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Vital Signs[c]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C)[d] (°F)[d]	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40.0 102.1-104.0	> 40.0 > 104.0
Tachycardia - beats per minute	101-115	116-130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute[e]	50-54	45-49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141-150	151-155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91-95	96-100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85-89	80-84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17-20	21-25	> 25	Intubation

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
[c] Subject should be at rest for all vital sign measurements.
[d] Oral temperature; no recent hot or cold beverages or smoking.
[e] When resting heart rate is between 60-100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or < 400 gms/24 hours	4-5 loose stools or 400-800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

U.S. Department of Health and Human Services, Food and Drug Administration, and Center for Biologics Evaluation and Research. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical 2007 Sep; 3-5

17.2 APPENDIX B: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists adverse events of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
Other	Acute cardiac failure
	Acute kidney failure
	Septic shock-like syndrome

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Seronegative Adults at High Risk of SARS-CoV-2 Exposure

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 3.0

Protocol Version Date: 18-Aug-2020

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted] r., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 2.0, dated 15Jun2020, to Version 3.0, dated 18-Aug-2020. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. The trial design has been modified as follows:
    a. A Phase 2 segment has been added to the study which will evaluate immunogenicity and safety in 400 subjects at two dose levels across three age groups. Safety and immunogenicity information from the Phase 2 segment will be used to determine the dose level for the Phase 3 segment of the study. The Phase 3 segment of the study has remained largely unchanged from the previous version of the protocol (v2.0).
    b. Relevant sections of the protocol have been updated to specify procedures for the Phase 2 segment of the study if they differ from the established procedures for the Phase 3 segment.
2. The eligibility criteria for the trial has been revised as follows:
    a. Additional description of the target study population has been included in the inclusion criteria to provide clarity related to enrollment of subjects “with high risk of exposure to SARS-CoV-2”. The revision to the inclusion criterion will provide clarity to the investigator regarding the types of subjects to be recruited.
    b. The inclusion criterion that discusses reproductive capacity has been modified to include Intrauterine device or system under medically effective contraception with a failure rate of < 1% per year.
    c. Several eligibility criteria have been modified to be more inclusive:
        i. The exclusion of subjects with Hepatitis B, Hepatitis C and HIV has been modified to limit exclusion to subjects with a known history of uncontrolled HIV.
        ii. The exclusion criterion related to medical conditions has been modified to permit subjects who have had non-metastatic prostate cancer not requiring treatment.
        iii. The exclusion criterion related to primary immunodeficiencies has been modified to permit subjects with conditions including hypothyroidism, Hashimoto’s thyroiditis and vitiligo.
        iv. The exclusion of ongoing smoking or vaping has been removed as per the recommendation of the DSMB chair, as these patients may be at higher risk for severe COVID-19 and may benefit from a future efficacious vaccine.
3. The schedule of events has been revised as follows:
    a. A separate Schedule of Events has been added for the Phase 2 segment of the study.
    b. Collection of safety blood samples (complete blood count, serum chemistry, urinalysis) has been moved from the Phase 3 segment of the study, where they were originally proposed by Inovio to be performed on a subset of subjects, to the Phase 2 segment of the study.

c. Implementation of a diary for collection of solicited AEs and injection site reactions has been moved from the Phase 3 segment of the study, where they were intended to be collected on a subset of subjects, to the Phase 2 segment of the study.

d. The timepoints for collection of cellular and humoral samples have been revised and it has been clarified that cellular samples will be collected in Cell Preparation Tubes (CPT) vacutainers.

e. The timeframes for performing the COVID-19 assessment and convalescent visits have been clarified.

f. Vital signs to be performed at the acute COVID-19 assessment and convalescent visits have been revised to enable the visit to be performed from the subject's vehicle or via telemedicine, if appropriate and allowable per site procedures.

g. The post-dose 2 in person visit has been modified to occur on Day 42 as opposed to Day 56, as Day 42 is the preferred immunogenicity collection timepoint. A phone call will occur on Day 56.

4. Background information has been updated based on current disease statistics and to provide additional rationale for the trial design. Additional safety data has been included from the Phase 1 study and additional information has been included related to risks of INO-4800 and the CELLECTRA® 2000 device.
5. Additional description of the investigational product, active (INO-4800) and placebo (SSC-0001), to be used for the Phase 2 and Phase 3 segments was provided. The description of the product within the protocol remains current for the Phase 2 segment of the study. The Phase 3 segment product will be matched product, both in 2 mL vials with 1.1 mL fill volumes.
6. Additional description has been provided regarding the device's essential performance requirements and administration procedure. Text clarifying that readministration is not permitted has been included.
7. The protocol has been revised to include the allowance of telemedicine for regularly scheduled visits should a subject have suspected or confirmed COVID-19 in order to make the visits more convenient to subjects and safe for site staff.
8. Clarification around rescreening of previously screen failed subjects has been included.
9. A restriction around receipt of hydroxychloroquine as prophylaxis has been added.
10. In the Phase 3 segment of the study, an additional at-home saliva collection has been added in the case where a subject develops a fever or experiences any symptoms suggestive of COVID-19. Clarification has also been included regarding storage of saliva collected at home.
11. Detail has been provided regarding referral of subjects to a primary care physician or medical treatment facility for treatment of COVID-19 disease as well as the expectations around obtaining test results, treatments, diagnostics, etc. from said facility.
12. The protocol has been clarified to reflect that, aside from grading of injection site reactions, the assessment of AE and laboratory abnormalities will be performed using the Common Terminology Criteria for Adverse Events, version 5.0. This has been removed as an Appendix from the document.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Seronegative Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 40 centers in the US

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 disease in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Approximately 6578 seronegative subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (SSC-0001) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0

Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6178 subjects 18 years of age and older will be randomized at a 1:1 ratio to receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001). See Table 2 and Figure 1. A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be ≥ 65 years of age.

Table 2: Phase 3 Segment Dose Groups

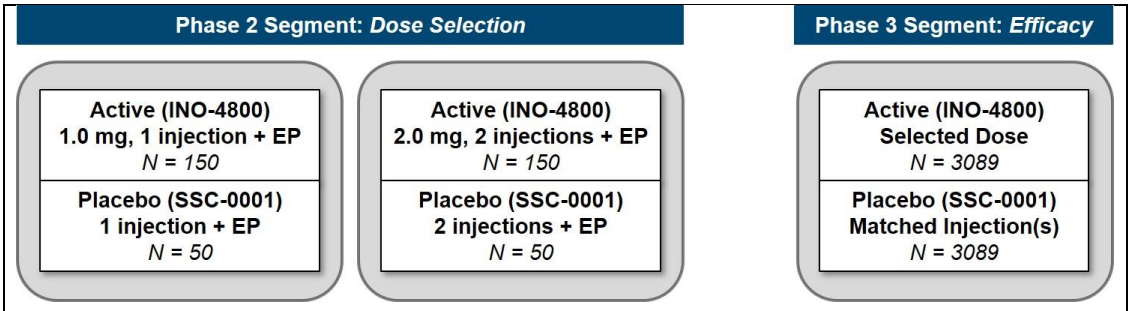
Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	Total Dose (mg)
INO-4800	3089	0, 28	TBD	TBD	TBD
Placebo	3089	0, 28	TBD	0	0
Total	**6178**				

TBD, to be determined based on the Phase 2 segment optimal dose selection

This segment of the trial is case-driven. Among seronegative subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6178 seronegative subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell

	numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the time to symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease
5. Evaluate the cellular and humoral immune response to INO-4800	5a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 5b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the immunological profile by assessing both antibody response and T cell immune response	1a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 1b. Antigen-specific cellular immune response measured by flow cytometry

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4). Assays such as Binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a Participant Diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing and RT-PCR. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff

6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);

g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
    - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;

n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: Dose level to be determined, each ID injection(s) of INO-4800 followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Placebo: Number of injections to be determined, each ID injection(s) of SSC-0001 followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swab)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits. The targeted physical exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltiod muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swab and saliva specimens at COVID-19 assessment and convalescent visits.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or via telemedicine and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test. Additional instructions for this visit will be provided in a separate study manual.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[n]	COVID-19 convalescent visit[o]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[p]	X[p]
Height and Weight	X																
CBC with differential[c]	X														X		
Chemistry[c]	X														X		
HIV Serology		X															
Urinalysis Routine[d]	X														X		
Pregnancy Test[e]	X	X			X										X		
INO-4800 or Placebo + EP[f]		X			X												
Download EP Data[g]			X			X											
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X					X		X		X				X		X
Humoral Samples[j]		X					X		X		X				X		X
SARS-CoV-2 Serology[l]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Saliva)[l]	X	X		X	X		X	X	X	X	X	X	X	X	X	X[m]	X[m]

a. Screening assessment occurs from -30 days to -1 day of Day 0.

b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits. The targeted physical exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltiod muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 CPT tubes, each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood). Cellular samples collected for all subjects at Day 0 pre-dose and Week 6; collected for approximately 10% of subjects at other indicated visits.
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva will be collected at study visits and bi-weekly at home between office visits. In-office collection time points for Screening, Day 0, Day 28, EOS and COVID-19 visits will be tested at the time of collection. All other stored saliva specimens will be selectively tested if a SARS-CoV-2 serology test becomes positive. The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.
m. Nasal swab and saliva specimens.
n. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or via telemedicine and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test. Additional instructions for this visit will be provided in a separate study manual.
o. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

The lack of available therapy in conjunction with increasing numbers of global cases indicate that SARS-CoV-2 infection remains a serious unmet medical concern. Appropriate measures to prevent, control and treat existing and future infections are in dire need.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [1-3]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named “Wuhan-Hu-1.” The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [4, 5]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [6, 7], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, “COVID-19,” associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

The first case of COVID-19 in the U.S. was announced in Washington State on January 21, 2020 by the Washington State Department of Health and the U.S. Centers for Disease Control and Prevention (US CDC) [8]. It was a case of a traveler who had returned from Wuhan, China. Since that case was detected, human-to-human local transmission began (or continued from previously undetected infections) in the U.S., and as of July 27, 2020, over 4 million laboratory-confirmed US COVID-19 cases and nearly 150,000 US deaths due to COVID-19 have been reported in all 50 states and its territories [9]. Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [10].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [11], associated with substantial morbidity and mortality [12]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [9]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based

seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [3] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty

six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga, et al, summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [10].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [12]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [10].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow, et al observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses

commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of a dominant SARS-CoV-2 variant G614, which now comprises more than 80% of circulating global viral strains, and is reportedly associated with increased infectivity and spread [33], an effective prophylactic vaccine should ideally induce immunity against not only the D614 virus but also the G614 variants.

Hospitals can provide supportive care for those who are infected and develop severe illness. Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated.

The CDC recommends that dexamethasone be used in the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated based on a preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial [34].

Remdesivir has received Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [35].

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a phase 2b randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer [31] and is currently in two multinational phase 3 trials for that indication (NCT03185013 and NCT03721978) and several phase 2 trials for related and other indications. We have built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a phase 1 clinical study, the MERS-CoV coronavirus vaccine was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [36].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of

the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [37-46]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [45, 47]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [48]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [49].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [50]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [51]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens [51] for the activation of both cellular and humoral responses [52, 53]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [53]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [54, 55].

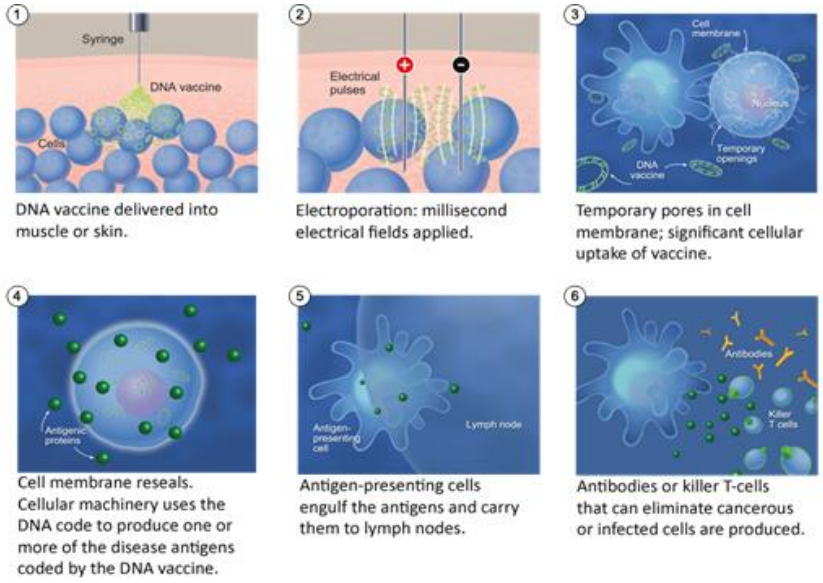
1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19 DISEASE

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA

vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [56-58].

Following intradermal injection, the Inovio Pharmaceuticals' constant current EP device [51] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [59]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [60].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11 adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of July 29, 2020, 17 related adverse events were reported cumulatively, of which all but one (Grade 2 injection site pruritus) was Grade 1 in severity.

Please refer to the Investigator's Brochure, which will include future updates through the life of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

Based on the review of the immunogenicity data from its Phase 1 trial in its initial cohort of 40 subjects 18-50 years of age, Inovio has determined that while the 1.0 mg and 2.0 mg doses of INO-4800 generate encouraging neutralizing antibody responses, the 2.0 mg dose appears to offer superior T-cell responses over the 1.0 mg dose as measured by INF-gamma responses in the initial Phase 1 cohort. Therefore, this Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), before selecting a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >6000 subjects.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. As such, there is a desire to demonstrate the ability of the vaccine to drive immune responses primarily within the first 6 weeks of the first dose, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In this study, 1.0 mg and 2.0 mg of vaccine is administered by ID injection and followed immediately by EP at Day 0 and Day 28. The dose selection is supported by the safety

profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) as well as our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial is to further down-select the 1.0mg and 2.0mg doses of INO-4800 for each age group in order to evaluate the optimal dose(s) in the efficacy Phase 3 segment.

1.4 POTENTIAL BENEFITS AND RISKS

As of July 29, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known. There may be potential benefits for prevention of COVID-19 disease, although efficacy remains unknown.

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 in combination with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID with EP using the CELLECTRA® 2000 Device[a]

Frequency[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain or tenderness
Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Severe administration site pain or tenderness

[a] Investigator's Brochure v2.0, dated 10-Apr-2020
[b] EU commission guideline on the SmPC September 2009 [61]

Additionally, the following potential risks are noted for use with the CELLECTRA® 2000 device (as per CELLECTRA® 2000 User Manual):

- Brief muscle contractions which may be uncomfortable.
- Injection site reactions: erythema, hematoma, pruritus, swelling, induration, tenderness, bruising/ecchymosis, laceration, or scab.
- Pain or soreness at the administration site.
- Temporary bleeding at the administration site.
- Anxiety related to the administration procedure.
- Vasovagal reaction/lightheadedness/dizziness related to the administration procedure.
- Muscle damage resulting in transient changes in creatine phosphokinase.

As of June 30, 2020, there have been no AEs associated with EP errors or failures.

Please refer to the Investigator's Brochure and User Manual, which will include future updates through the life of the study.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Approximately 6578 seronegative subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study, a Phase 2 segment and a Phase 3 segment. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo (SSC-0001). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6178 subjects 18 years of age and older will be randomized at a 1:1 ratio to receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001). A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be ≥ 65 years of age.

This segment of the trial is case-driven. Among seronegative subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%),

assuming a true efficacy of 60%. A sample size of 6178 subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs)

	1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the timing of symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease.
5. Evaluate the cellular and humoral immune response to INO-4800	5a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 5b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINT

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**

1. Evaluate the immunological profile by assessing both antibody response and T cell immune response	1a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 1b. Antigen-specific cellular immune response measured by flow cytometry

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing and RT-PCR. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-Cov-2 test result will be reviewed by the independent blinded EAC. The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (any source) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (any source) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
d. Significant acute renal, hepatic, or neurologic dysfunction,
e. Admission to an ICU, or
f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);

- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED SARS-COV-2 INFECTION

- Positive testing by SARS-CoV-2 RT-PCR assay (any source);
- With or without clinical signs or symptoms of COVID-19 disease.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment, solicited local and systemic AEs will be collected for 7 days following each dose.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as Binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household

8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
10. Others, if approved by the medical monitor;

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. **Note**: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;

- History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
- Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
- Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
- Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
- Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
- History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;

i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
   - Current or anticipated use of disease modifying doses of systemic 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);
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial

or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a

synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 1.1 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 1.1 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, 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, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP treatment consists of four pulses.
- An Array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The needle length that penetrates into the skin and tissue is approximately 3 mm.
- The CELLECTRA® 2000 generates four 52ms electrical current controlled DC pulses. The nominal current is set to 200mA ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance
- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device for ID administration is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Dose level to be determined, each ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: Dose level to be determined, each ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded throughout the trial. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 1.1 mL. SSC-0001 is supplied in 2-mL vials at a minimum volume of 1.1 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4.) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics and document any ongoing, pre-existing conditions;
- Collect socio-behavioral assessment information (Section 6.4);
- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9).

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, and any other past conditions,

as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or occurred within the 12 weeks prior to Screening. Subjects should be queried about any history of Hepatitis B and Hepatitis C. Any subject with a self-reported history of Hepatitis B or C who has clinically significant elevated liver enzymes at Screening will be excluded from the study based on inclusion criterion f. Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 and an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

Study visits occurring within 3 weeks of an acute COVID-19 visit with confirmed SARS-CoV-2 RT-PCR test may be conducted via telemedicine.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Review restrictions for injection and EP (Section 6.4.8);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR and send to lab for testing (Section 6.4.9);

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data (Section 6.4.1.1);
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide, saliva collection kit)
- Phase 2 segment only: Distribute diary

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);

Phase 2 segment only:
- Review diary (Section 6.4).

Phase 3 segment only:
- Remind subject to perform at-home saliva collection (Section 6.4.9).

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);

- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.10);
- Record current concomitant medications/treatments (Section 6.4.7);
- Phase 3 segment only: Remind subject to perform at-home saliva collection (Section 6.4.9).

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (except Day 294 visit) (Section 6.4.6);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR; (Section 6.4.9);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;

- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test (Section 6.4);
- Collect blood for CBC with differential and serum chemistry(Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or via telemedicine and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR. Additional instructions will be provided to sites in a separate study manual.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect nasal swab and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect nasal swab and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects
- Explain the clinical trial
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description
  - Eligibility criteria for entering the clinical trial
  - Clinical trial treatments and follow-up procedures description
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives
    - Potential benefits and risks
    - Discomforts/inconveniences
    - Subject's rights and responsibilities

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a 4-digit site code and a 4-digit subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms. The targeted physical exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 Assessment and Convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

At Screening and at visits specified in the Schedule of Events (Tables 3 and 4), blood samples will be collected for safety assessments. Approximately mL 270-360 of blood will be drawn from each subject over the course of the study. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening.

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

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 immediately prior to any dosing and at the subject's last visit. 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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol only. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the phone calls on Day 7 and Day 35, respectively. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be collected.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

- Injection of IP (INO-4800 or placebo)
- Insertion of the array into the subject's skin
- Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after drug has been administered

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed (i.e. EP given)?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Readministration of drug (i.e. protocol-specified drug has already been delivered) is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28.

Phase 3 segment:

Subjects will receive a two-dose regimen of either one or two 1.0mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28. The dose level will be determined based on results of the study's Phase 2 segment.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

Samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4.) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. Administration (injection) site reactions and administration site pain will be evaluated starting 30 minutes following injection/EP. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

September 2007 "FDA Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires, 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood) be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood and 8 mL serum is required on Day 0 prior to 1st dose. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

The additional immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay, flow cytometry and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene expression, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

6.4.7 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) must be recorded on CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.8) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.8 RESTRICTIONS

Subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature >38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine for any condition, or any other drug intended as COVID-19 prophylaxis during the trial, or as supplementary COVID-19 prophylaxis post-dose.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.9 SARS-COV-2 TESTING

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic, subject's vehicle, or via telemedicine. During this visit, a nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. For a remote visit, the subject will self-collect the nasal and saliva samples and the site will provide instructions to properly handle the samples (e.g. transport of samples to the clinic, shipment of samples to the testing laboratory, etc). If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on saliva specimens collected at Screening, Day 0, Day 28 and Day 393 or EOS visit. During other in-office study visits (see Table 4: Schedule of Events), saliva samples will be collected by clinical personnel and stored on site until further instruction. Bi-weekly home self-collections of saliva will be done by subjects, between study visits according to the Schedule of Events. Subjects will be provided instructions to properly handle these specimens (e.g. transport of samples to the clinic at the next in-person visit, shipment of samples directly to the testing laboratory, etc). Testing will be performed on selected saliva samples if the subject's SARS-CoV-2 serology test becomes positive.

The Day 0 and Day 28 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

If, at any time during the trial, either the SARS-CoV-2 antibody or RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or via telemedicine, a nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay.

6.4.10 COVID-19 DISEASE MONITORING

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of higher than 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff

should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. For subjects in the Phase 3 segment, a home saliva sample should be self-collected each day for up to 3 days by the subject until the COVID-19 assessment visit. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or via telemedicine. Procedures to be performed during this visit will be specified in a separate study manual.

Subjects with a confirmed COVID-19 diagnosis prior to dose 2 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell or stabilization of symptoms and follow up testing according to Institutional policy.

Subjects who require medical care for COVID-19 disease (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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)

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
- 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
- Confirmed COVID-19 disease

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 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.
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE..
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE.
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event.
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF.

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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment
- Changes in laboratory parameters
- Local and systemic injection site review; special attention will be paid to the examination of the injection site

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

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 further administration of the investigational product in the clinical trial
- 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment.
- Any Grade 4 AEs related to study treatment.
- Any report of anaphylaxis related to study treatment.
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.
Email: [redacted]
Cell Phone: [redacted]
Inovio Medical Monitor: [redacted]Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the PI until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 number (SID)
- Investigational product(s) (IP) and/or study device
- Investigator causal relationship to the IP(s) and/or study 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 AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 CTCAE.

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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the PI. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the PI (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the PI (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose 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 dose administrations, 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. 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 a Pregnancy Information Collection Consent Form 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, infection, and timing of symptom resolution. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq .70/(.70+k)$ *vs.* H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population will be primary for the analysis of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analysis of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analysis of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

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

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI for efficacy exceeds 30%, and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 **SECONDARY ANALYSES**

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The secondary efficacy endpoint regarding timing of symptom resolution will be analyzed with Kaplan-Meier plots by treatment group.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for these immunogenicity analyses.

8.5.3 **SAFETY ANALYSES**

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to Phase.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.5.6 INTERIM ANALYSES

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

8.5.7 MULTIPLICITY

Not applicable; there is one hypothesis that will be tested.

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

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

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean titers and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for immunogenicity analyses.

8.5.9.2 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 160 observed cases will be required to provide 90% power to declare the vaccine efficacious (>30%), utilizing the methodology described in Section 8.5.1 and assuming a true efficacy of 60%. A sample size of 6178 subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

Phase 3 Segment

Subjects will be randomized (1 INO-4800:1 Placebo).

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes

(e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

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

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses

- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will meet approximately once per month, at a minimum. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip

report. Report any significant unresolved problems immediately to the Sponsor.

- Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
- Assure that the trial facilities, including the pharmacy, continue to be acceptable.
- Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and Department of Defense, Joint Program Executive Office is providing funding for the study. Clinical trial insurance has been taken out according to 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 per 21 CFR Part 54.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium
PT	Preferred Term
RBC	Red blood cell

REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization

16.0 REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020; 92(4):401-402.
2. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020; 91:264-266.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223):497-506.
4. GenBank. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. https://www.ncbi.nlm.nih.gov/nuccore/MN908947
5. Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. *Nat Commun* 2020; 11(1):2601.
6. World Health Organization. Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance. In; 2020.
7. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report. 2020
8. Centers for Disease Control and Prevention. First Travel-related Case of 2019 Novel Coronavirus Detected in United States. In; January 21, 2020.
9. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. In; 2020.
10. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020.
11. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. In; March 11, 2020.
12. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *The New England journal of medicine* 2020.
13. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. *JAMA Intern Med* 2020.
14. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol* 2020; 41(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly* 2020; 2(8):113-122.
17. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; 395(10223):514-523.
18. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *The New England journal of medicine* 2020; 382(10):970-971.
19. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2020; 25(17).
20. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature medicine* 2020; 26(5):672-675.

21. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020; 27(2).
22. Centers for Disease Control and Prevention. Symptoms of Coronavirus. March 2020. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
23. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *The New England journal of medicine* 2020.
24. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. *BMJ* 2020; 369:m1375.
25. Centers for Disease Control and Prevention. COVID-19 Pandemic Planning Scenarios. July 27, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html
26. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003; 300(5627):1966-1970.
27. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361(9371):1767-1772.
28. Tsang TK, Cowling BJ, Fang VJ, Chan KH, Ip DK, Leung GM, et al. Influenza A Virus Shedding and Infectivity in Households. *J Infect Dis* 2015; 212(9):1420-1428.
29. Seow J, Graham C, Merrick B, Acors S, Steel KJA, Hemmings O, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *medRxiv* 2020:2020.2007.2009.20148429.
30. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020.
31. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Front Immunol* 2020; 11:827.
32. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell* 2020; 181(7):1489-1501 e1415.
33. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell* 2020.
34. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *The New England journal of medicine* 2020.
35. US FDA. Fact Sheet for Patients And Parents/Caregivers Emergency Use Authorization (EUA) Of Veklury® (remdesivir) For Coronavirus Disease 2019 (COVID-19) In; 2020.
36. Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019; 19(9):1013-1022.
37. Suschak JJ, Williams JA, Schmaljohn CS. Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Hum Vaccin Immunother* 2017; 13(12):2837-2848.
38. Manickan E, Karem KL, Rouse BT. DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology? *Crit Rev Immunol* 2017; 37(2-6):483-498.
39. Porter KR, Raviprakash K. DNA Vaccine Delivery and Improved Immunogenicity. *Curr Issues Mol Biol* 2017; 22:129-138.
40. Li L, Petrovsky N. Molecular mechanisms for enhanced DNA vaccine immunogenicity. *Expert Rev Vaccines* 2016; 15(3):313-329.
41. Marc MA, Dominguez-Alvarez E, Gamazo C. Nucleic acid vaccination strategies against infectious diseases. *Expert Opin Drug Deliv* 2015; 12(12):1851-1865.

42. Grunwald T, Ulbert S. Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases. *Clin Exp Vaccine Res* 2015; 4(1):1-10.
43. Tregoning JS, Kinnear E. Using Plasmids as DNA Vaccines for Infectious Diseases. *Microbiol Spectr* 2014; 2(6).
44. Williams JA. Improving DNA vaccine performance through vector design. *Curr Gene Ther* 2014; 14(3):170-189.
45. Liu MA. DNA vaccines: an historical perspective and view to the future. *Immunol Rev* 2011; 239(1):62-84.
46. Wahren B, Liu MA. DNA Vaccines: Recent Developments and the Future. *Vaccines (Basel)* 2014; 2(4):785-796wahren.
47. Ledgerwood JE, Graham BS. DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases. *Hum Vaccin* 2009; 5(9):623-626.
48. Keefer MC, Graham BS, Belshe RB, Schwartz D, Corey L, Bolognesi DP, et al. Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network. *AIDS Res Hum Retroviruses* 1994; 10(12):1713-1723.
49. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *Medrxiv Preprint* 2020.
50. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol* 2006; 13(11):1267-1277.
51. Prud'homme GJ, Glinka Y, Khan AS, Draghia-Akli R. Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases. *Curr Gene Ther* 2006; 6(2):243-273.
52. Hirao LA, Wu L, Khan AS, Hokey DA, Yan J, Dai A, et al. Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques. *Vaccine* 2008; 26(25):3112-3120.
53. Rosati M, Valentin A, Jalah R, Patel V, von Gegerfelt A, Bergamaschi C, et al. Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation. *Vaccine* 2008; 26(40):5223-5229.
54. Curcio C, Khan AS, Amici A, Spadaro M, Quaglino E, Cavallo F, et al. DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice. *Cancer Gene Ther* 2008; 15(2):108-114.
55. Ugen KE, Kutzler MA, Marrero B, Westover J, Coppola D, Weiner DB, et al. Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation. *Cancer Gene Ther* 2006; 13(10):969-974.
56. 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. *The New England journal of medicine* 2017.
57. Tebas P, Kraynyak KA, Patel A, Maslow JN, Morrow MP, Sylvester AJ, et al. Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers. *J Infect Dis* 2019.
58. De Rosa SC, Edupuganti S, Huang Y, Han X, Elizaga M, Swann E, et al. Robust antibody and cellular responses induced by DNA-only vaccination for HIV. *JCI Insight* 2020; 5(13).
59. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science* 2020.
60. Patel A, Walters J, Reuschel EL, Schultheis K, Parzych E, Gary EN, et al. Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model. *bioRxiv* 2020:2020.2007.2028.225649.

61. European Commission. Directorate-General: A Guideline on Summary of Product Characteristics (SmPC). In: EMA; 2009.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
Other	Acute cardiac failure
	Acute kidney failure
	Septic shock-like syndrome

Signature Page for VV-TMF-00448 v3.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 19-Aug-2020 03:39:54 GMT+0000

Signature Page for VV-TMF-00448 v3.0

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Seronegative Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 4.0

Protocol Version Date: 13-Nov-2020

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 3.0, dated 18Aug2020, to Version 4.0, dated 13-Nov-2020. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. The following device information has been clarified in the protocol, upon request from the United States Food and Drug Administration (U.S. FDA):
    a. Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 device have been expanded to include theoretical risks, especially as related to the device.
    b. Discussions regarding the needle depth and total maximum energy delivered during electroporation have been added.
    c. The description of the administration procedure has been updated to clarify that reinjection of the IP or delivery of a second EP in tissue is not permitted.
2. The restrictions have been updated to limit subjects from participating in any other interventional trials while they are enrolled in this trial.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Healthy Seronegative Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 40 centers in the US

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 disease in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Approximately 6578 seronegative subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (SSC-0001) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0

Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6178 subjects 18 years of age and older will be randomized at a 1:1 ratio to receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001). See Table 2 and Figure 1. A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be ≥ 65 years of age.

Table 2: Phase 3 Segment Dose Groups

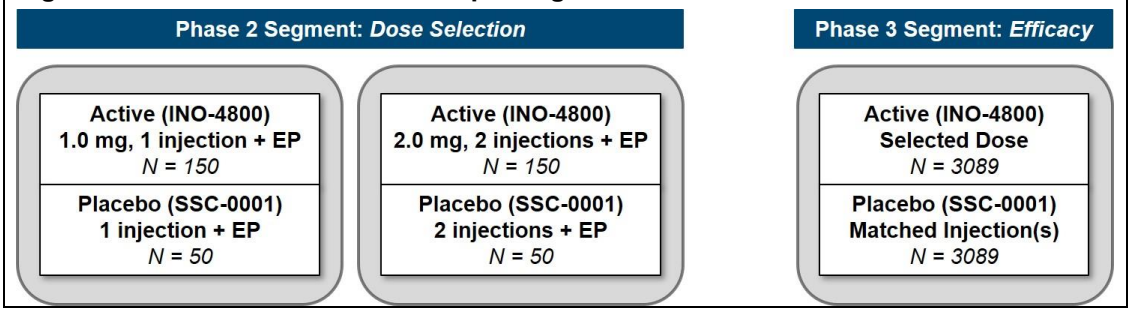
Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	Total Dose (mg)
INO-4800	3089	0, 28	TBD	TBD	TBD
Placebo	3089	0, 28	TBD	0	0
Total	**6178**				

TBD, to be determined based on the Phase 2 segment optimal dose selection

This segment of the trial is case-driven. Among seronegative subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6178 seronegative subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews
For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**

1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the time to symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease
5. Evaluate the cellular and humoral immune response to INO-4800	5a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 5b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the immunological profile by assessing both antibody response and T cell immune response	1a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 1b. Antigen-specific cellular immune response measured by flow cytometry

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding enzyme-linked immunosorbent assay (ELISA), pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a Participant Diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing and RT-PCR. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field

9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)

- Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
- Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
- Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
- Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
- History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;

i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
   - Current or anticipated use of disease modifying doses of systemic 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);
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment Active Investigational Product: Dose level to be determined, each ID injection(s) of INO-4800 followed immediately by EP administered at Day 0 and Day 28 (±3 days) Placebo: Number of injections to be determined, each ID injection(s) of SSC-0001 followed immediately by EP administered at Day 0 and Day 28 (±3 days)
Formulation: INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swab)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits. The targeted physical exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltiod muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swab and saliva specimens at COVID-19 assessment and convalescent visits.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or via telemedicine and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[n]	COVID-19 convalescent visit[o]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[p]	X[p]
Height and Weight	X																
CBC with differential[c]	X														X		
Chemistry[c]	X														X		
HIV Serology		X															
Urinalysis Routine[d]	X														X		
Pregnancy Test[e]	X	X			X										X		
INO-4800 or Placebo + EP[f]		X			X												
Download EP Data[g]			X			X											
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X					X		X		X				X		X
Humoral Samples[j]		X					X		X		X				X		X
SARS-CoV-2 Serology[l]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Saliva)[l]	X	X		X	X		X	X	X	X	X	X	X	X	X	X[m]	X[m]

a. Screening assessment occurs from -30 days to -1 day of Day 0.

b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits. The targeted physical exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltiod muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 CPT tubes, each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood). Cellular samples collected for all subjects at Day 0 pre-dose and Week 6; collected for approximately 10% of subjects at other indicated visits.
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva will be collected at study visits and bi-weekly at home between office visits. In-office collection time points for Screening, Day 0, Day 28, EOS and COVID-19 visits will be tested at the time of collection. All other stored saliva specimens will be selectively tested if a SARS-CoV-2 serology test becomes positive. The Day 0 and Day 28 RT-PCR results will not be required prior to dosing on that day.
m. Nasal swab and saliva specimens.
n. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or via telemedicine and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
o. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

The lack of available therapy in conjunction with increasing numbers of global cases indicate that SARS-CoV-2 infection remains a serious unmet medical concern. Appropriate measures to prevent, control and treat existing and future infections are in dire need.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [1-3]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [4, 5]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [6, 7], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

The first case of COVID-19 in the U.S. was announced in Washington State on January 21, 2020 by the Washington State Department of Health and the U.S. Centers for Disease Control and Prevention (US CDC) [8]. It was a case of a traveler who had returned from Wuhan, China. Since that case was detected, human-to-human local transmission began (or continued from previously undetected infections) in the U.S., and as of July 27, 2020, over 4 million laboratory-confirmed US COVID-19 cases and nearly 150,000 US deaths due to COVID-19 have been reported in all 50 states and its territories [9]. Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [10].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [11], associated with substantial morbidity and mortality [12]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [9]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based

seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [3] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-

six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [10].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [12]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [10].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses

commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of a dominant SARS-CoV-2 variant G614, which now comprises more than 80% of circulating global viral strains, and is reportedly associated with increased infectivity and spread [33], an effective prophylactic vaccine should ideally induce immunity against not only the D614 virus but also the G614 variants.

Hospitals can provide supportive care for those who are infected and develop severe illness. Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated.

The CDC recommends that dexamethasone be used in the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated based on a preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial [34].

Remdesivir has received Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [35].

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 2b randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer [36] and is currently in two multinational Phase 3 trials for that indication (NCT03185013 and NCT03721978) and several Phase 2 trials for related and other indications. We have built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV coronavirus vaccine was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [37].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of

the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [38-47]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [46, 48]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [49]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [50].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [51]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [52]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens [52] for the activation of both cellular and humoral responses [53, 54]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [54]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [55, 56].

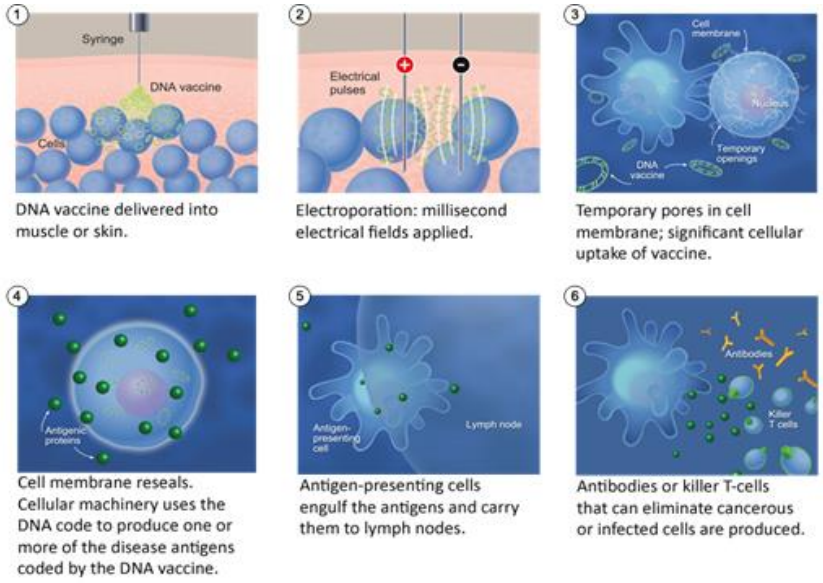
1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19 DISEASE

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA

vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [57-59].

Following ID injection, the Inovio Pharmaceuticals' constant current EP device [52] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [60]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [61].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11 adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of July 29, 2020, 17 related adverse events were reported cumulatively, of which all but one (Grade 2 injection site pruritus) was Grade 1 in severity.

Please refer to the Investigator's Brochure, which will include future updates through the life of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

Based on the review of the immunogenicity data from its Phase 1 trial in its initial cohort of 40 subjects 18-50 years of age, Inovio has determined that while the 1.0 mg and 2.0 mg doses of INO-4800 generate encouraging neutralizing antibody responses, the 2.0 mg dose appears to offer superior T-cell responses over the 1.0 mg dose as measured by INF-gamma responses in the initial Phase 1 cohort. Therefore, this Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), before selecting a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >6000 subjects.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. As such, there is a desire to demonstrate the ability of the vaccine to drive immune responses primarily within the first 6 weeks of the first dose, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In this study, 1.0 mg and 2.0 mg of vaccine is administered by ID injection and followed immediately by EP at Day 0 and Day 28. The dose selection is supported by the safety

profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) as well as our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial is to further down-select the 1.0mg and 2.0mg doses of INO-4800 for each age group in order to evaluate the optimal dose(s) in the efficacy Phase 3 segment.

1.4 RISKS AND POTENTIAL BENEFITS

As of October 9, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile through the duration of the study.

1.4.1 POTENTIAL BENEFITS

There may be potential benefits for prevention of COVID-19 disease, although efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness
Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v3.0, dated 25-Aug-2020
[b] EU commission guideline on the SmPC September 2009 [62]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of June 30, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction
- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of June 30, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)
- Cardiac arrhythmias (product-related); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion ‘g’ in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g. electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;
- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;

- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that "Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment" is an exclusion criterion ('h') in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 OVERALL BENEFIT/RISK CONCLUSION

In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio's DNA platform across all of its products, and INO-4800's Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies participation in the Phase 2/3 trial.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Approximately 6578 seronegative subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study, a Phase 2 segment and a Phase 3 segment. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-

4800) or 1 or 2 injections of placebo (SSC-0001). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6178 subjects 18 years of age and older will be randomized at a 1:1 ratio to receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001). A minimum of 15% of the total sample size of subjects will be 51-64 years of age, and a minimum of 5% of the total sample size of subjects will be ≥ 65 years of age.

This segment of the trial is case-driven. Among seronegative subjects, a total of 160 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6178 subjects is expected to be required to achieve the 160 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12-months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS))

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity	2a. Incidence of non-severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until EOS

	2c. Incidence of deaths due to COVID-19 starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 infection	3. Incidence of virologically-confirmed SARS-CoV-2 infections starting 14 days after completion of the 2-dose regimen until EOS
4. Evaluate the timing of symptom resolution in subjects who develop COVID-19 disease	4. Days to symptom resolution in subjects developing COVID-19 disease.
5. Evaluate the cellular and humoral immune response to INO-4800	5a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 5b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINT

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the immunological profile by assessing both antibody response and T cell immune response	1a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 1b. Antigen-specific cellular immune response measured by flow cytometry

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing and RT-PCR. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-Cov-2 test result will be reviewed by the independent blinded EAC. The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (any source) with fever (temperature of 100.4ºF/38.0ºC or higher), or

- Positive testing by SARS-CoV-2 RT-PCR assay (any source) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
d. Significant acute renal, hepatic, or neurologic dysfunction,
e. Admission to an ICU, or
f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED SARS-COV-2 INFECTION

- Positive testing by SARS-CoV-2 RT-PCR assay (any source);
- With or without clinical signs or symptoms of COVID-19 disease.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2. SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment, solicited local and systemic AEs will be collected for 7 days following each dose.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as Binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
    9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
    10. Others, if approved by the medical monitor;
f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;

- Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
  - hormonal contraception including implants, injections or oral;
  - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
  - intrauterine device or intrauterine system;
  - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg at Screening;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);

- Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
- Current or anticipated use of disease modifying doses of systemic 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);
- History of solid organ or bone marrow transplantation;
- History of or current receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact

medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 1.1 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 1.1 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.
- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [63].

- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Dose level to be determined, each ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: Dose level to be determined, each ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded throughout the trial. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 1.1 mL. SSC-0001 is supplied in 2-mL vials at a minimum volume of 1.1 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device

prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4.) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics and document any ongoing, pre-existing conditions;
- Collect socio-behavioral assessment information (Section 6.4);
- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or occurred within the 12 weeks prior to Screening. Subjects should be queried about any history of Hepatitis B and Hepatitis C. Any subject with a self-reported history of Hepatitis B or C who has clinically significant elevated liver enzymes at Screening will be excluded from the study based on inclusion criterion f. Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 and an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

Study visits occurring within 3 weeks of an acute COVID-19 visit with confirmed SARS-CoV-2 RT-PCR test may be conducted via telemedicine.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Section 6.4.6);

- Review restrictions for injection and EP (Section 6.4.8);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR and send to lab for testing (Section 6.4.9);

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data;
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide, saliva collection kit)
- Phase 2 segment only: Distribute diary

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);

Phase 2 segment only:
- Review diary (Section 6.4).

Phase 3 segment only:
- Remind subject to perform at-home saliva collection (Section 6.4.9).

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.10);
- Record current concomitant medications/treatments (Section 6.4.7);
- Phase 3 segment only: Remind subject to perform at-home saliva collection (Section 6.4.9).

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (except Day 294 visit) (Section 6.4.6);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR; (Section 6.4.9);
- Provide supplies for subject to use at home, as required (e.g. saliva collection kit).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test (Section 6.4);
- Collect blood for CBC with differential and serum chemistry(Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.9);

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or via telemedicine and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect nasal swab and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);

- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect nasal swab and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.9).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.9).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a 4-digit site code and a 4-digit subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms. The targeted physical

exam is optional at the COVID-19 assessment visit if the visit is conducted via telemedicine.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 Assessment and Convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

At Screening and at visits specified in the Schedule of Events (Tables 3 and 4), blood samples will be collected for safety assessments. Approximately mL 270-360 of blood will be drawn from each subject over the course of the study. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening.

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

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 immediately prior to any dosing and at the subject's last visit. 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 subject is pregnant prior to completing the specified

dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol only. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the phone calls on Day 7 and Day 35, respectively. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be collected.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin
3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections should be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of either one or two 1.0mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP with CELLECTRA® 2000 at Day 0 and Day 28. The dose level will be determined based on results of the study's Phase 2 segment.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

Samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. Administration (injection) site reactions and administration site pain will be evaluated starting 30 minutes following injection/EP. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

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

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires, 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood) be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood and 8 mL serum is required on Day 0 prior to 1st dose. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

The additional immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay, flow cytometry and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene expression, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

6.4.7 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) must be recorded on CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.8) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.8 RESTRICTIONS

Subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature >38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine for any condition, or any other drug/vaccine intended as COVID-19 prophylaxis during the trial, or as supplementary COVID-19 prophylaxis post-dose.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.9 SARS-CoV-2 Testing

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic, subject's vehicle, or via telemedicine. During this visit, a nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. For a remote visit, the subject will self-collect the nasal and saliva samples and the site will provide instructions to properly handle the samples (e.g. transport of samples to the clinic, shipment of samples to the testing laboratory, etc). If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on saliva specimens collected at Screening, Day 0, Day 28 and Day 393 or EOS visit. During other in-office study visits (see Table 4: Schedule of Events), saliva samples will be collected by clinical personnel and stored on site until further instruction. Bi-weekly home self-collections of saliva will be done by subjects, between study visits according to the Schedule of Events. Subjects will be provided instructions to properly handle these specimens (e.g. transport of samples to the clinic at the next in-person visit, shipment of samples directly to the testing laboratory, etc). Testing will be performed on selected saliva samples if the subject's SARS-CoV-2 serology test becomes positive.

The Day 0 and Day 28 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

If, at any time during the trial, either the SARS-CoV-2 antibody or RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or via telemedicine, a nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay.

6.4.10 COVID-19 Disease Monitoring

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of higher than 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. For subjects in the Phase 3 segment, a home saliva sample should be self-collected each day for up to 3 days by the subject until the COVID-19 assessment visit. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or via telemedicine.

Subjects with a confirmed COVID-19 diagnosis prior to dose 2 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell or stabilization of symptoms and follow up testing according to Institutional policy.

Subjects who require medical care for COVID-19 disease (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;
- Confirmed COVID-19 disease.

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 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF.

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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;

- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the PI to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

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 further administration of the investigational product in the clinical trial;
- 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment;
- Any Grade 4 AEs related to study treatment;
- Any report of anaphylaxis related to study treatment;
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB

recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.
Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the PI until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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 AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 CTCAE.

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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the PI. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the PI (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the PI (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose 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 dose administrations, 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. 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 a Pregnancy Information Collection Consent Form 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, infection, and timing of symptom resolution. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq .70/(.70+k)$ *vs.* H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population will be primary for the analysis of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analysis of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analysis of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

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

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding 95% confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI for efficacy exceeds 30%, and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-values.

The secondary efficacy endpoint regarding timing of symptom resolution will be analyzed with Kaplan-Meier plots by treatment group.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for these immunogenicity analyses.

8.5.3 SAFETY ANALYSES

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to Phase.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.5.6 INTERIM ANALYSES

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

8.5.7 MULTIPLICITY

Not applicable; there is one hypothesis that will be tested.

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

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

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean titers and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

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

The PP population will be used for immunogenicity analyses.

8.5.9.2 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 160 observed cases will be required to provide 90% power to declare the vaccine efficacious (>30%), utilizing the methodology described in Section 8.5.1 and assuming a true efficacy of 60%. A sample size of 6178 subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline

characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

Phase 3 Segment

Subjects will be randomized (1 INO-4800:1 Placebo).

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

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

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will meet approximately once per month, at a minimum. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip

report. Report any significant unresolved problems immediately to the Sponsor.

- Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
- Assure that the trial facilities, including the pharmacy, continue to be acceptable.
- Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and Department of Defense, Joint Program Executive Office is providing funding for the study. Clinical trial insurance has been taken out according to 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 per 21 CFR Part 54.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization

16.0 REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020; 92(4):401-402.
2. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020; 91:264-266.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223):497-506.
4. GenBank. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. https://www.ncbi.nlm.nih.gov/nuccore/MN908947
5. Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. *Nat Commun* 2020; 11(1):2601.
6. World Health Organization. Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance. In; 2020.
7. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report. 2020
8. Centers for Disease Control and Prevention. First Travel-related Case of 2019 Novel Coronavirus Detected in United States. In; January 21, 2020.
9. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. In; 2020.
10. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020.
11. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. In; March 11, 2020.
12. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *The New England journal of medicine* 2020.
13. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. *JAMA Intern Med* 2020.
14. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol* 2020; 41(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly* 2020; 2(8):113-122.
17. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; 395(10223):514-523.
18. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *The New England journal of medicine* 2020; 382(10):970-971.
19. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2020; 25(17).
20. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature medicine* 2020; 26(5):672-675.

21. Liu Y, Gayle AA, Wilder-Smith A, Rocklov J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020; 27(2).
22. Centers for Disease Control and Prevention. Symptoms of Coronavirus. March 2020. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
23. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *The New England journal of medicine* 2020.
24. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. *BMJ* 2020; 369:m1375.
25. Centers for Disease Control and Prevention. COVID-19 Pandemic Planning Scenarios. July 27, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html
26. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003; 300(5627):1966-1970.
27. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361(9371):1767-1772.
28. Tsang TK, Cowling BJ, Fang VJ, Chan KH, Ip DK, Leung GM, et al. Influenza A Virus Shedding and Infectivity in Households. *J Infect Dis* 2015; 212(9):1420-1428.
29. Seow J, Graham C, Merrick B, Acors S, Steel KJA, Hemmings O, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *medRxiv* 2020:2020.2007.2009.20148429.
30. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020.
31. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Front Immunol* 2020; 11:827.
32. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell* 2020; 181(7):1489-1501 e1415.
33. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell* 2020.
34. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *The New England journal of medicine* 2020.
35. US FDA. Fact Sheet for Patients And Parents/Caregivers Emergency Use Authorization (EUA) Of Veklury® (remdesivir) For Coronavirus Disease 2019 (COVID-19) In; 2020.
36. 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.
37. Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019; 19(9):1013-1022.
38. Suschak JJ, Williams JA, Schmaljohn CS. Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity. *Hum Vaccin Immunother* 2017; 13(12):2837-2848.
39. Manickan E, Karem KL, Rouse BT. DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology? *Crit Rev Immunol* 2017; 37(2-6):483-498.
40. Porter KR, Raviprakash K. DNA Vaccine Delivery and Improved Immunogenicity. *Curr Issues Mol Biol* 2017; 22:129-138.

41. Li L, Petrovsky N. Molecular mechanisms for enhanced DNA vaccine immunogenicity. *Expert Rev Vaccines* 2016; 15(3):313-329.
42. Marc MA, Dominguez-Alvarez E, Gamazo C. Nucleic acid vaccination strategies against infectious diseases. *Expert Opin Drug Deliv* 2015; 12(12):1851-1865.
43. Grunwald T, Ulbert S. Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases. *Clin Exp Vaccine Res* 2015; 4(1):1-10.
44. Tregoning JS, Kinnear E. Using Plasmids as DNA Vaccines for Infectious Diseases. *Microbiol Spectr* 2014; 2(6).
45. Williams JA. Improving DNA vaccine performance through vector design. *Curr Gene Ther* 2014; 14(3):170-189.
46. Liu MA. DNA vaccines: an historical perspective and view to the future. *Immunol Rev* 2011; 239(1):62-84.
47. Wahren B, Liu MA. DNA Vaccines: Recent Developments and the Future. *Vaccines (Basel)* 2014; 2(4):785-796wahren.
48. Ledgerwood JE, Graham BS. DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases. *Hum Vaccin* 2009; 5(9):623-626.
49. Keefer MC, Graham BS, Belshe RB, Schwartz D, Corey L, Bolognesi DP, et al. Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network. *AIDS Res Hum Retroviruses* 1994; 10(12):1713-1723.
50. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *Medrxiv Preprint* 2020.
51. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol* 2006; 13(11):1267-1277.
52. Prud'homme GJ, Glinka Y, Khan AS, Draghia-Akli R. Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases. *Curr Gene Ther* 2006; 6(2):243-273.
53. Hirao LA, Wu L, Khan AS, Hokey DA, Yan J, Dai A, et al. Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques. *Vaccine* 2008; 26(25):3112-3120.
54. Rosati M, Valentin A, Jalah R, Patel V, von Gegerfelt A, Bergamaschi C, et al. Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation. *Vaccine* 2008; 26(40):5223-5229.
55. Curcio C, Khan AS, Amici A, Spadaro M, Quaglino E, Cavallo F, et al. DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice. *Cancer Gene Ther* 2008; 15(2):108-114.
56. Ugen KE, Kutzler MA, Marrero B, Westover J, Coppola D, Weiner DB, et al. Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation. *Cancer Gene Ther* 2006; 13(10):969-974.
57. 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. *The New England journal of medicine* 2017.
58. Tebas P, Kraynyak KA, Patel A, Maslow JN, Morrow MP, Sylvester AJ, et al. Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers. *J Infect Dis* 2019.
59. De Rosa SC, Edupuganti S, Huang Y, Han X, Elizaga M, Swann E, et al. Robust antibody and cellular responses induced by DNA-only vaccination for HIV. *JCI Insight* 2020; 5(13).

60. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science* 2020.
61. Patel A, Walters J, Reuschel EL, Schultheis K, Parzych E, Gary EN, et al. Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model. *bioRxiv* 2020:2020.2007.2028.225649.
62. European Commission. Directorate-General: A Guideline on Summary of Product Characteristics (SmPC). In: EMA; 2009.
63. Diehl MC, Lee JC, Daniels SE, Tebas P, Khan AS, Giffear M, et al. Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers. *Hum Vaccin Immunother* 2013; 9(10):2246-2252.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
Other	Acute cardiac failure
	Acute kidney failure
	Septic shock-like syndrome

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 5.0

Protocol Version Date: 2-Apr-2021

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 4.0, dated 13-Nov-2020, to Version 5.0, dated 2-Apr-2021. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. The approximate number of sites and regions has been updated;
2. The number of subjects to be enrolled in the Phase 3 segment has been increased to a total of 7116 subjects, inclusive of 6714 SARS-CoV-2 seronegative and 402 SARS-CoV-2 seropositive subjects. The randomization ratio of active to placebo was increased from 1:1 to 2:1 in the Phase 3 segment of the trial in order to increase the likelihood that subjects will receive INO-4800. This resulted in a change to the sample size, which was increased to 6714 seronegative subjects in the Phase 3 segment, and a change in the number of COVID-19 cases needed for the primary endpoint analysis to 149;
    a. The seropositive group of 402 subjects was added to evaluate primarily the safety of INO-4800 in those who have been previously infected with SARS-CoV-2 in order that future vaccinations under Emergency Use Authorization or post-licensure can be administered INO-4800 without the requirement of prior testing for serostatus;
    b. Two age groups will be evaluated in the Phase 3 segment: 18-50 years of age and 51 years or older. A minimum of 10% of the overall enrollment will be subjects ≥65 years of age. Age has been added as a stratification factor to the Phase 3 segment of the trial;
3. For the Phase 3 segment, two formal interim analyses were added and are planned for when 50% and 75% of the COVID-19 cases accrue, respectively, and criteria were added for crossing subjects over from placebo to active product;
4. The following secondary objectives have been removed for the Phase 3 segment of the trial:
    a. Time to symptom resolution in subjects developing COVID-19;
    b. Evaluation of efficacy in prevention of SARS-CoV-2 infection.
        i. Bi-weekly self-collection of saliva samples by subjects has also been removed from the protocol as this will no longer be necessary to support this objective.
5. The following secondary and exploratory endpoints have been added for the Phase 3 segment of the trial:
    a. Secondary objective to assess vaccine efficacy in subjects with prior SARS-CoV-2 infection;
    b. Exploratory endpoint to monitor vaccine efficacy against SARS-CoV-2 variants;
    c. Exploratory objective to evaluate the prevention of SARS-CoV-2 asymptomatic infection.
    d. Exploratory objective to assess antibody persistence;
6. In the Phase 3 segment of the trial, the requirement for use of medically effective contraception will be required only during the 1-month dosing period. Urine pregnancy testing for women of childbearing potential will be required at Screening and prior to each dose to ensure that pregnant women are not dosed during the trial;
7. The inclusion criterion that defines the target population at high risk of SARS-CoV-2 was refined to include additional examples and allows for the judgment of the Investigator in determining whether a subject falls into this high risk category for SARS-CoV-2 exposure;
8. The subject eligibility criteria for the Phase 3 segment have been further modified to include those with selected medical conditions that place them at higher risk for severe COVID-19. The protocol will allow subjects with cancer, chronic kidney disease, chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension, neurologic conditions including stroke or cerebrovascular disease that do not impact cognition, diabetes

(type 1 or 2), hypertension, heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies, HIV infection (CD4 count > 200 cells/mm^3 or undetectable viral load), liver disease, obesity (BMI ≥ 30 kg/m2), sickle cell disease or thalassemia, smoking (current or former smoker) as long as these conditions have been stable without requiring hospitalization or significant medication changes within 3 months prior to planned dosing. This has also been added to the Phase 3 segment of the study as a stratification factor at randomization;

9. The dose of INO-4800 for the Phase 3 segment of the study has been preliminarily indicated as 1.0 mg. However, upon review of the Phase 2 data by age group, if the immunogenicity of the 2.0 mg dose of INO-4800 is substantially superior to that of 1.0 mg dose, then the clinical protocol will be updated accordingly;
10. Safety labs at Screening and Day 393 for the Phase 3 segment were removed based on safety data from the Phase 1 study and the blinded safety data from the Phase 2 segment of the current study. Consequently, the requirement for safety labs within the normal range or deemed not clinically significant by the Investigator were removed from the inclusion criteria;
11. SARS-CoV-2 PCR testing specimen will be collected on Day 0 instead of at Screening. Any subject who is suspected to have COVID-19 at Day 0 will not be dosed. If a subject's Day 0 specimen subsequently tests positive, they will not receive the second dose of Investigational Product (IP). Additional PCR testing timepoints have been removed, as SARS-CoV-2 infection in seronegative subjects will be determined based on serology sample collection at in-office visits throughout the trial;
12. The cellular immunology sample collection timepoints have been modified and will be collected at only selected Phase 3 sites. Further details regarding the testing plan have been included;
13. The primary endpoint for Phase 3 will be assessed using nasopharyngeal swabs. Furthermore, the language has been updated to disallow subject self-collection of SARS-CoV-2 RT-PCR samples that contribute to the primary endpoint. The case definition has been revised to indicate that specimens contributing to the primary endpoint will be tested at a central laboratory, with the exception when a subject is hospitalized, at which testing at a local lab is permissible if obtaining a specimen for central laboratory testing is not possible.
14. Genotyping has been added to the SARS-CoV-2 testing at the COVID-19 assessment visit to attempt to detect infection with potential SARS-CoV-2 variants;
15. It has been clarified that for the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. A pausing rule has been added to pause the trial based on a vaccine-to-placebo case split of 8:0 for severe COVID-19 disease, as confirmed by the DSMB;
16. Collection of solicited injection site reactions and systemic AEs using a diary in the Phase 3 segment has been added to be administered at selected sites to further establish the safety and tolerability of INO-4800;
17. Instructions related to cleaning and disinfecting the CELLECTRA® 2000 Pulse Generators and ID Applicators have been included in Section 5.1.2;
18. The exclusion criterion and restrictions around receipt of investigational (including EUA or local equivalent authorization) or licensed COVID-19 vaccine have been clarified. Selective unblinding for the purposes of supporting any decision to receive EUA vaccine will not be permitted;
19. A description of the Phase 2 group level unblinded analysis details has been added;
20. The IP information has been updated to include INO-4800 vials with a fill volume of 0.4 mL;
21. Additional Adverse Events of Special Interest (AESI) have been added to the table in Appendix A.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 50 centers globally. Final country list to be determined.

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (SSC-0001) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0
Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 1.0 mg) or placebo (SSC-0001). See Table 2 and Figure 1. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥51 years of age. Also, a minimum of 10% of the total sample size will be ≥65 years of age.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per U.S. Center for Disease Control (CDC) criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

Table 2: Phase 3 Segment

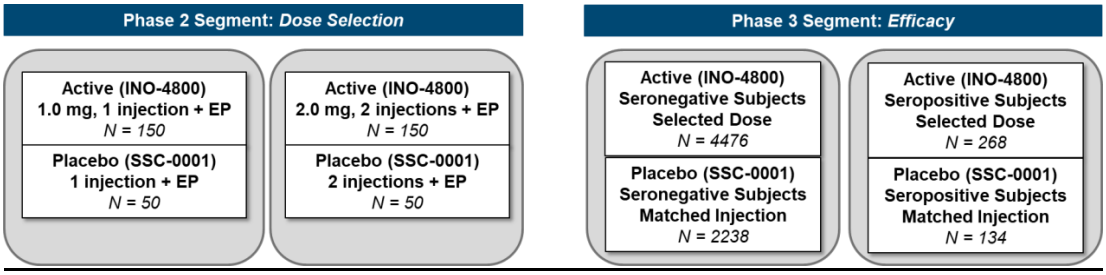
Treatment Arm	Sero status	Expected Number of Subjects	Expected Number of Subjects by Age Group		Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose of INO-4800 (mg)
			18-50	51+[b]					
INO-4800	Seroneg	4476	2238	2238	0, 28	1	1.0	1.0[a]	2.0[a]
	Seropos	268	134	134					
Placebo	Seroneg	2238	1119	1119	0, 28	1	0	0	0
	Seropos	134	67	67					
Total	**Seroneg**	6714	3357	3357					
	Seropos	402	201	201					
Total		7116							

[a]1.0mg is the presumed dose for Phase 3
[b]at least 711 subjects will be ≥65 years of age

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 3b. Antigen-specific cellular immune response such as measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding enzyme-linked immunosorbent assay (ELISA), pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot-forming assay (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms per the case definition or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Phase 2 segment: Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Phase 3 segment: Subjects at high risk for SARS-CoV-2 exposure including subjects at high risk for severe COVID-19 who are 18 years and older.

Inclusion Criteria: Phase 2 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly

5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;
        iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria: Phase 3 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary

staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria: Phase 2 segment

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;

d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Exclusion Criteria: Phase 3 segment

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (this criterion only applies after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, after which this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
    - Current or anticipated use of disease modifying doses of systemic 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) or others;
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: One 1.0mg ID injection of INO-4800 followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Placebo: One ID injection of SSC-0001 followed immediately by EP administered at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swabs)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltoid muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swabs and saliva specimens at COVID-19 assessment and convalescent visits. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, in the subject’s vehicle or at the subject’s home and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)[k]	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[l]	COVID-19 convalescent visit[m]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[n]	X[n]
Height and Weight	X																
HIV Serology		X															
Pregnancy Test[c]	X	X			X												
INO-4800 or Placebo + EP[d]		X			X												
Download EP Data[e]			X			X											
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[g]		X					X				X				X	X[r]	X
Humoral Samples[h]		X					X				X				X	X[r]	X
SARS-CoV-2 Serology[i]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Nasopharyngeal swabs)		X														X[o]	
Distribute Diary[p]			X			X											
Review/Collect Diary[q]				X	X		X										

a. Screening assessment occurs from -30 days to -1 day of Day 0. Screening and Day 0 visits may be combined if eligibility is able to be confirmed prior to dosing. If so, all assessments for Screening and Day 0 must be performed at the combined visit.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.

c. In women of childbearing potential. Urine pregnancy test at all indicated visits.
d. Intradermal injection(s) in skin preferably over deltoid region, or alternately over anterolateral quadriceps region, followed by EP at Day 0 and Day 28.
e. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
f. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
g. On Day 0, cellular sampling requires 64 mL of whole blood prior to 1st dose. At all other time points, collect 32 mL of whole blood. Cellular samples will be collected at selected clinical sites (estimated to include 711 subjects)
h. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce four serum aliquots of 2 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each.
i. SARS-CoV-2 antibody.
j. The Day 0 RT-PCR results will not be required prior to dosing on that day.
k. Day 42 visit must occur at least 10 days after Day 28 visit.
l. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or at a home visit and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
m. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization
n. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.
o. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
p. Diaries to be used at selected sites only (estimated to include 711 subjects).
q. Diary should be reviewed at the 14-day post-dose phone call or visit and collected at the next in-office visit.
r. When possible, cellular and humoral immunology samples will be collected. Cellular samples will be collected at selected sites only.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Given the continued number of cases globally, SARS-CoV-2 infections remain a serious unmet medical concern. Appropriate measures to prevent SARS-CoV-2 infections, including its variants, are not yet widely available.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [2-4]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [5, 6]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [7, 8], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [9].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [10], associated with substantial morbidity and mortality [11]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [12]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid

test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [4] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities

include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [9].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [9].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19, however there are several vaccines that are available under Emergency Use Authorization (EUA) in the United States and other countries. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of new strains of SARS-CoV-2, an effective prophylactic vaccine ideally induces immunity against not only SARS-CoV-2 Wuhan-Hu-

1 but also its variants. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for additional vaccines for prevention of SARS-CoV-2 infections.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 3 (REVEAL1) randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer (NCT03185013) and several Phase 2 trials for related and other indications and several Phase 2 trials for related and other indications. We have additionally built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV vaccine candidate was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [33].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [34-43]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [42, 44]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [45]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research

in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [46].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [47]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

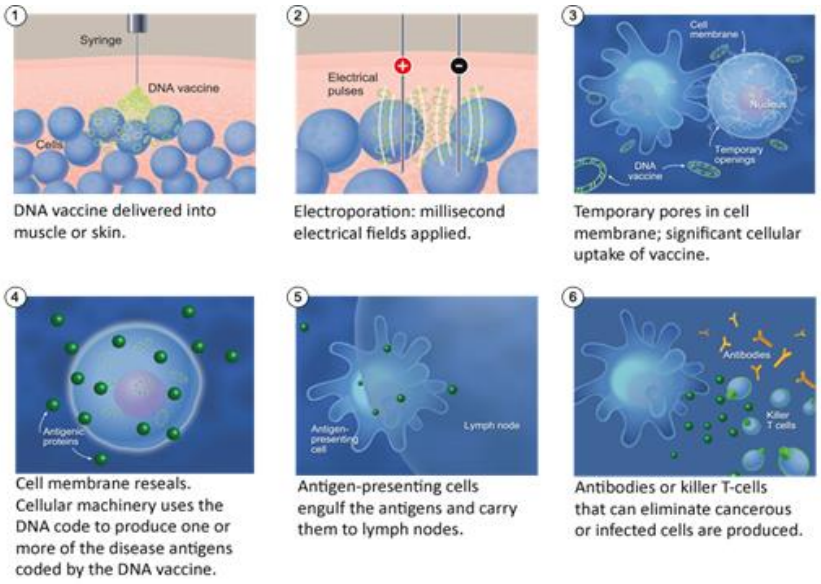
Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [48]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens for the activation of both cellular and humoral responses [49, 50]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [50]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [51, 52].

1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 Wuhan-Hu-1 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [53-55].

Following ID injection, the Inovio Pharmaceuticals' EP device [48] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES FOLLOWING VACCINATION WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [56]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [57].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11

adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of July 29, 2020, 17 related adverse events were reported cumulatively, of which all but one (Grade 2 injection site pruritus) was Grade 1 in severity.

Please refer to the Investigator's Brochure, which will include future updates through the duration of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

This Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), to enable selection of a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >7000 subjects.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. Based on Inovio's extensive experience developing vaccine candidates against infectious diseases via the ID route ([54], [33]), a 2-dose regimen was considered to be optimal, based on the balanced humoral and cellular responses obtained 2 weeks post-dose 2, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In this study, 1.0 mg and 2.0 mg of vaccine is administered by ID injection and followed immediately by EP at Day 0 and Day 28. The selection of the doses to test in Phase 2 is supported by the safety profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) as well as our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial is to further select the 1.0 mg and 2.0 mg doses of INO-4800 for each age group in order to evaluate the optimal vaccination regimen in the efficacy Phase 3 segment. The final decision between the two doses by age group relies on safety, immunogenicity as well as the practicality of

administration. The 1.0 mg and 2.0 mg doses in the Phase 1 study had a similar safety profile. The available blinded Phase 2 data has not revealed any significant safety signals. The 1.0 mg dose is favored over the 2.0 mg dose based on the greater convenience of a single injection per day. Therefore, unless the 2.0 mg dose provides substantially superior immunogenicity when compared to the 1.0 mg dose by age group in Phase 2, we anticipate that the 1.0 mg dose will offer the better balance of safety, immunogenicity and ease of administration.

1.4 RISKS AND POTENTIAL BENEFITS

As of Dec 31, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile through the duration of the study.

1.4.1 POTENTIAL BENEFITS

The efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness
Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v3.0, dated 25-Aug-2020
[b] EU commission guideline on the SmPC September 2009 [58]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of June 30, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction

- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of June 30, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)
- Cardiac arrhythmias (product-related); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g., electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;
- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;

- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that "Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment" is an exclusion criterion ('h') in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 OVERALL BENEFIT/RISK CONCLUSION

While EUA vaccines are currently becoming available in many countries, the global availability to the general population remains limited. In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio's DNA platform across all of its products, and INO-4800's Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies the conduct of the Phase 2/3 trial.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo (SSC-0001). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 1mg) or placebo (SSC-0001). Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥ 51 years of age. Also, a minimum of 10% of the total sample size will be ≥65 years of age.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence of or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per CDC criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease, that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The

actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for Phase 3, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints

1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINTS

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	Phase 2 Exploratory Endpoints
1. Evaluate the expanded immunological profile of antibody	1a. Antigen-specific cellular immune response measured by flow cytometry.

response and T cell immune response	1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 3b. Antigen-specific cellular immune response measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the independent blinded EAC.

The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat

- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

*Local lab results will be accepted if the subject is hospitalized and a sample is not able to be obtained for analysis at central lab.

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
d. Significant acute renal, hepatic, or neurologic dysfunction,
e. Admission to an ICU, or
f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR SARS-COV-2 ASYMPTOMATIC INFECTION

Positive testing by SARS-CoV-2 serologic assay (performed at central lab);

- Without clinical signs or symptoms of COVID-19 disease since the previous negative serologic test.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

4.1.1 PHASE 2 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
    9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
    10. Others, if approved by the medical monitor;
f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        - hormonal contraception including implants, injections or oral;
        - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);

- intrauterine device or intrauterine system;
- abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 PHASE 3 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
    2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
    4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
    9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
    10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.
f. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;

3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
   - **i.** hormonal contraception including implants, injections or oral;
   - **ii.** two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
   - **iii.** intrauterine device or intrauterine system;
   - **iv.** abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

4.2.1 PHASE 2 SEGMENT

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);

- Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the prior 6 months;
- Current or anticipated use of disease modifying doses of systemic 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);
- History of solid organ or bone marrow transplantation;
- History of or current receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.2.2 **PHASE 3 SEGMENT**

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:

   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);

- Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
- Current or anticipated use of disease modifying doses of systemic 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) or others;
- History of solid organ or bone marrow transplantation;
- History of or current receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;

k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;

l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);

m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;

n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing

address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL or 1.1 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 1.1 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 **CELLECTRA® 2000**

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.
- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [59].

- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles. The Pulse Generator and ID Applicator are reusable components. These components should be cleaned and disinfected prior to each subject's use according to the Cleaning and Maintenance procedure in the User Manual. The Pulse Generator and ID Applicator have been validated for up to 30 cleaning and disinfection cycles based on a maximum of 30 subjects being treated in a day. Therefore, the Pulse Generator and ID Applicator's use should be limited to 30 subjects in a day. Any potential risk of damage to the device due to cleaning and disinfection for more than 30 cycles has not been validated. Always inspect the device before use according to the instructions in the Maintenance section of the User Manual.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: One 1.0mg ID injection of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One ID injection of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded throughout the trial. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

It is not deemed appropriate to unblind a subject's treatment assignment for the purpose of assisting the subject in making a decision regarding receipt a different COVID-19 vaccine (emergency use or licensed vaccine). Subjects should be advised that without efficacy data, INO-4800 has not been proven to be more protective than placebo in the

prevention of COVID-19 and SARS-CoV-2 infection. Therefore, unblinding will not provide any meaningful information to inform a decision of receiving a different COVID-19 vaccine.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for such an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 or 1.1 mL. SSC-0001 is supplied in 2-mL vials at a minimum volume of 1.1 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4.) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration. Screening and Day 0 visits may be on the same day if eligibility is able to be confirmed prior to

randomization. If so, all assessments for Screening and Day 0 must be performed at the combined visit.

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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics;
- Collect socio-behavioral assessment information (Section 6.4);
- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.6);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect urine for pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.8).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or having occurred within 3 months prior to Screening. Subjects should be queried about any history of Hepatitis B, Hepatitis C and HIV.

In the Phase 3 segment, subjects with a self-reported history of Hepatitis B or C must provide documentation of liver enzymes that are not significantly elevated within the past 3 months. If such a report of liver enzyme testing is not available, this testing should be performed at Screening. Subjects with a history of Hepatitis C without cirrhosis who have completed treatment and have proof of an undetectable viral load at least 12 weeks following treatment may be enrolled and do not require liver enzymes within the past months.

Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 or an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed

consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);
- Review restrictions for injection and EP (Section 6.4.7);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR (Day 0 only) (Section 6.4.8);
- Collect diary from Day 0 dose during Day 28 visit only(for selected sites only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data;
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide);

- Phase 2 segment: Distribute diary;
- Phase 3 segment, for selected sites: Distribute diary.

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);

Phase 2 segment only:
- Review diary (Section 6.4).

Phase 3 segment only:
- Review diary (for selected sites)(Section 6.4);

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5);

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect diary from Day 28 visit (for selected sites only);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.9);
- Record current concomitant medications/treatments (Section 6.4.6);

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 Day 201 visit only; Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test (Section 6.4);

Phase 2 segment:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);

- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5).

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or at a home visit and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR testing from the central lab. A local RT-PCR result will be considered acceptable in the case where a subject is hospitalized and a sample for central lab analysis is not able to be obtained, if it was obtained using. an assay performed by a laboratory accredited according to standards set by a national or regional accreditation body.

If a local lab is used to confirm the case, the report from the laboratory must be provided.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 only:

- Collect whole blood and serum for cellular and humoral immunology assessment, where possible (Phase 3 cellular immunology collection at selected sites only)(Section 6.5)
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (Section 6.4.8).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 2 segment only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a 4-digit site code and a 4-digit subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 assessment and convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

Blood samples will be collected at visits specified in the Schedule of Events (Tables 3 and 4). A total of approximately mL 245-330mL of blood will be drawn from each subject over the course of the study (inclusive of relevant safety and immunology samples at regular study visits per Tables 3 and 4). If the subjects is evaluated at COVID-19 visits, an additional volume of approximately 85-120mL will be collected. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening (Phase 2 segment only).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Pregnancy Testing:

Pregnancy testing will be performed on women of childbearing potential (WOCBP). All women will be assumed to be of childbearing potential unless they are:

- Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
- Women who are surgically sterile or have a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of a vasectomy, subjects should wait six (6) months post-vasectomy to be considered sterile.

Phase 2: For WOCBP, a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit.

Phase 3: For WOCBP, a urine pregnancy test will be obtained at Screening and will be performed immediately prior to any dosing.

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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol and at selected sites (estimated to include 711 subjects) in the Phase 3 segment. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the next study phone call or visit and collected at the next in-person study visit. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be assessed.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin
3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of each injection site with CELLECTRA® 2000

at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections must be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of the injection site with CELLECTRA® 2000 at Day 0 and Day 28. The dose level will be determined based on results of the study's Phase 2 segment.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

In Phase 2, samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4.) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. All subjects will be observed for 30 minutes following the IP administration procedure for immediate AEs. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

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

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

[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 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) must be recorded on CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.7) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.7 RESTRICTIONS

In the Phase 2 segment of the trial, subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1.1). In the Phase 3 segment of the trial, subjects should refrain from becoming pregnant until receipt of the last dose of investigation product by using appropriate contraceptive measures (See Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature ≥38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine or any other drug/vaccine intended as COVID-19 prophylaxis during the trial. If a subject informs the site of their intent to receive another COVID-19 vaccine (emergency use or licensed vaccine), the subject should be informed that the safety and effectiveness of receiving INO-4800 followed by another COVID-19 vaccine has not been studied. In the Phase 3 segment, subjects should be reminded that if and when appropriate, the Sponsor would provide INO-4800 to those who received placebo in the trial.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.8 SARS-CoV-2 Testing

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic or subject's vehicle or at the subject's home. During this visit, nasal swabs and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed. If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on nasopharyngeal specimens collected at Day 0. The Day 0 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

If, at any time during the trial, either the SARS-CoV-2 antibody or an RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or in the subject's home, nasopharyngeal swabs will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed on the sample(s) collected at the COVID-19 assessment visit.

6.4.9 COVID-19 Disease Monitoring

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3

segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of ≥ 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or in the subject's home.

Subjects with a confirmed COVID-19 diagnosis, per the case definition outlined in Section 3.7, prior to dose 2 or who have a positive SARS-CoV-2 PCR test at Day 0 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell, or with sequelae that appear to be permanent.

Subjects who require medical care for COVID-19 (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

6.5 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires 32 mL of whole blood be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood for cellular sampling and 8 mL serum for humoral sampling is required on Day 0 prior to 1st dose. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

Humoral samples will be collected on all subjects and cellular samples will be collected at selected sites (from approximately 711 subjects). Both humoral and cellular analysis will be conducted in the first 102 subjects age 18-50 and in the first 102 subjects age 51 and older enrolled at the sites that are selected for cellular sample collection. In addition, cellular and humoral samples will be analyzed on all subjects with COVID-19 when samples are available.

The immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene expression or flow cytometry, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;

- Confirmed COVID-19 disease.

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

<u>Clarification of Serious Adverse Events (SAEs)</u>

- Death 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF.

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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;
- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

The Investigator will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the Investigator'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 further administration of the investigational product in the clinical trial;
- Has accompanying or inducing symptoms or signs;
- Is judged by the Investigator 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The Investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment;
- Any Grade 4 AEs related to study treatment;
- Any report of anaphylaxis related to study treatment;
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

In the case of suspected Severe COVID-19 cases, the trial will be paused if a vaccine-to-placebo case split yields a relative risk with a 90% confidence interval lower bound >1. The minimum case split corresponding to this criterion is 8:0. In this scenario, the trial will pause until at least one additional case is accrued and the DSMB can review the data and make a recommendation regarding continued enrollment in the trial.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.
Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the Investigator until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 Investigator 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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

Investigators should use correct medical terminology/concepts when recording AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 Investigator will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with CTCAE.

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 Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator 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.

Investigators 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 Investigator 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 Investigator'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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the Investigator. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects in Phase 2 who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

Subjects in Phase 3 who are pregnant or expect to become pregnant prior to the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

The Investigator 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 dose administrations, must not be performed. The Investigator 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 Investigator if their partner becomes pregnant until study completion. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign a Pregnancy Information Collection Consent Form to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The site will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If an Investigator is contacted by the male subject or his pregnant partner, the Investigator 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's

primary endpoint is the incidence of virologically-confirmed COVID-19 disease in subjects who are SARS-CoV-2 seronegative at baseline starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, and cases among baseline SARS-CoV-2 seropositive subjects. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern efficacy against variants, efficacy against asymptomatic infection, and binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% among baseline SARS-CoV-2 seronegative subjects will be tested with H_0: $p \geq .70/(.70+k)$ *vs.* H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population among those who are baseline SARS-CoV-2 seronegative will be primary for the analyses of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status of the subjects. Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

Among subjects who are SARS-CoV-2 seronegative at baseline, the primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.022 and the corresponding lower bound of the two-sided 95.6% CI for efficacy exceeds 30% (alpha-level adjusted for interim analyses, see Section 8.5.6), and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but with 95% CIs and without the hypothesis test p-value.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects and by baseline SARS-CoV-2 serostatus.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint.. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

8.5.3 **SAFETY ANALYSES**

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.6 INTERIM ANALYSES

For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The two-sided type I error of 0.05 will not be adjusted for possible early stopping due to this aspect.

For the Phase 2 segment, group-level unblinded summaries of the immunogenicity and safety data will be produced once Week 6 visit immunology data and Week 8 visit safety data are complete for all subjects who have not discontinued, while maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all subjects who have not discontinued with remaining visits through the final visit. These summaries will allow the Sponsor to have results for the purposes of dose selection for the Phase 3

portion. No subject-level immunogenicity data will be produced, and subject-level immunogenicity data will not be available in the clinical trial database until all other clinical trial data are finalized at the end of the trial. No safety summary will be provided if the total number of subjects who experience the event of interest is greater than 0 and the count of the number of subjects with the event in a given treatment group relative to the total produces a percentage less than 3%, for a given summary. The group-level unblinded production of the summaries will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

For the Phase 3 segment, there are two planned formal interim efficacy analyses: one at 50% (75 cases) and one at 75% (112 cases) of the total required for the primary endpoint (149 cases). The Lan-DeMets O'Brien-Fleming approximate alpha-spending function will be used for the efficacy and futility boundaries. As such, the first interim analysis will utilize a one-sided nominal alpha of 0.0016, and the second interim analysis will utilize a one-sided nominal alpha of 0.0092. The final analysis will utilize a one-sided nominal alpha of 0.022. The DSMB will be responsible for the interim evaluations. The unblinded interim analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

If the prespecified criteria for efficacy above are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until 4500 subjects have 6 months of safety follow-up. At that point, the trial would be unblinded, and subjects who received placebo will be offered the active product.

8.5.7 **MULTIPLICITY**

There is one primary hypothesis that will be tested. As there are two interim analyses of the primary endpoint, the type I error rate will be controlled at two-sided 0.05 by using the Lan-DeMets O'Brien-Fleming approximate alpha-spending function (see Section 8.5.6).

8.5.8 **MISSING VALUES**

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 **EXPLORATORY ANALYSES**

8.5.9.1 Efficacy

Phase 3 segment

The exploratory efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but with a 95% CI and without the hypothesis test p-value.

8.5.9.2 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline increases in antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean fold-rises and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.3 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 149 observed cases among baseline SARS-CoV-2 seronegative subjects will be required to provide 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60% and utilizing the methodology described in Section 8.5.1 and Section 8.5.6 . A sample size of 6714 baseline SARS-CoV-2 seronegative subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

Phase 3 Segment

Subjects will be randomized (2 INO-4800:1 Placebo). Randomization will be stratified according to two factors, each with two levels: a) age-group age category (18-50 years vs. ≥51 years) on Day 0, and b) presence or absence on Day 0 of underlying medical conditions that increase risk of severe COVID-19 disease, per US CDC criteria.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

- Submit continuing review reports to the IRB/REB/EC as required, and request re-review and approval of the clinical trial at least once a year during the conduct of the clinical trial;
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects;
- Notify the IRB/REB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events;
- Obtain approval from the IRB/REB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required;
- Submit reports on, and reviews of, the clinical trial and its progress to the IRB/REB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines;

- Maintain a file of clinical trial-related information (refer to clinical trial files) that includes all correspondence with the IRB/REB/EC;
- Notify the IRB/REB/EC when the clinical trial is completed (i.e., after the last clinical trial visit of the final clinical trial subject);
- After clinical trial completion (within three [3] months is recommended), provide the IRB/REB/EC with a final report on the clinical trial.

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion.

If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
  - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
  - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and Department of Defense, Joint Program Executive Office is providing funding for the study. Clinical trial insurance has been taken out according to 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 per 21 CFR Part 54.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot-forming assay
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

16.0 REFERENCES

1. Centers for Disease Control and Prevention. *People with Certain Medical Conditions*. March 29, 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
2. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. **92**(4): p. 401-402.
3. Hui, D.S., et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.* Int J Infect Dis, 2020. **91**: p. 264-266.
4. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
5. GenBank. *Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome*. 2020; Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.
6. Smith, T.R.F., et al., *Immunogenicity of a DNA vaccine candidate for COVID-19.* Nat Commun, 2020. **11**(1): p. 2601.
7. World Health Organization, *Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance.* 2020.
8. World Health Organization, *Novel Coronavirus (2019-nCoV) Situation Report*. 2020.
9. Wiersinga, W.J., et al., *Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.* JAMA, 2020.
10. World Health Organization, *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. March 11, 2020.
11. Zou, L., et al., *SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.* N Engl J Med, 2020.
12. Center for Systems Science and Engineering at Johns Hopkins University, *COVID-19 Dashboard*. 2020.
13. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Intern Med, 2020.
14. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* Chin J Epidemiol, 2020. **41**(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
17. Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* Lancet, 2020. **395**(10223): p. 514-523.
18. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.* N Engl J Med, 2020. **382**(10): p. 970-971.
19. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020.* Euro Surveill, 2020. **25**(17).
20. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020. **26**(5): p. 672-675.

21. Liu, Y., et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus.* J Travel Med, 2020. **27**(2).
22. Centers for Disease Control and Prevention. *Symptoms of Coronavirus*. 2020 March 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
23. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* N Engl J Med, 2020.
24. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ, 2020. **369**: p. m1375.
25. Centers for Disease Control and Prevention. *COVID-19 Pandemic Planning Scenarios*. July 10, 2020 July 20, 2020 July 27, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
26. Lipsitch, M., et al., *Transmission dynamics and control of severe acute respiratory syndrome.* Science, 2003. **300**(5627): p. 1966-70.
27. Peiris, J.S., et al., *Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.* Lancet, 2003. **361**(9371): p. 1767-72.
28. Tsang, T.K., et al., *Influenza A Virus Shedding and Infectivity in Households.* J Infect Dis, 2015. **212**(9): p. 1420-8.
29. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
30. Long, Q.X., et al., *Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.* Nat Med, 2020.
31. Diao, B., et al., *Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19).* Front Immunol, 2020. **11**: p. 827.
32. Grifoni, A., et al., *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.* Cell, 2020. **181**(7): p. 1489-1501 e15.
33. Modjarrad, K., et al., *Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial.* Lancet Infect Dis, 2019. **19**(9): p. 1013-1022.
34. Suschak, J.J., J.A. Williams, and C.S. Schmaljohn, *Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity.* Hum Vaccin Immunother, 2017. **13**(12): p. 2837-2848.
35. Manickan, E., K.L. Karem, and B.T. Rouse, *DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology?* Crit Rev Immunol, 2017. **37**(2-6): p. 483-498.
36. Porter, K.R. and K. Raviprakash, *DNA Vaccine Delivery and Improved Immunogenicity.* Curr Issues Mol Biol, 2017. **22**: p. 129-138.
37. Li, L. and N. Petrovsky, *Molecular mechanisms for enhanced DNA vaccine immunogenicity.* Expert Rev Vaccines, 2016. **15**(3): p. 313-29.
38. Marc, M.A., E. Dominguez-Alvarez, and C. Gamazo, *Nucleic acid vaccination strategies against infectious diseases.* Expert Opin Drug Deliv, 2015. **12**(12): p. 1851-65.
39. Grunwald, T. and S. Ulbert, *Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases.* Clin Exp Vaccine Res, 2015. **4**(1): p. 1-10.
40. Tregoning, J.S. and E. Kinnear, *Using Plasmids as DNA Vaccines for Infectious Diseases.* Microbiol Spectr, 2014. **2**(6).
41. Williams, J.A., *Improving DNA vaccine performance through vector design.* Curr Gene Ther, 2014. **14**(3): p. 170-89.
42. Liu, M.A., *DNA vaccines: an historical perspective and view to the future.* Immunol Rev, 2011. **239**(1): p. 62-84.

43. Wahren, B. and M.A. Liu, *DNA Vaccines: Recent Developments and the Future.* Vaccines (Basel), 2014. **2**(4): p. 785-796wahren.
44. Ledgerwood, J.E. and B.S. Graham, *DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases.* Hum Vaccin, 2009. **5**(9): p. 623-6.
45. Keefer, M.C., et al., *Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network.* AIDS Res Hum Retroviruses, 1994. **10**(12): p. 1713-23.
46. Wu, F., et al., *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.* Medrxiv Preprint, 2020.
47. Martin, J.E., et al., *A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial.* Clin Vaccine Immunol, 2006. **13**(11): p. 1267-77.
48. Prud'homme, G.J., et al., *Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.* Curr Gene Ther, 2006. **6**(2): p. 243-73.
49. Hirao, L.A., et al., *Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques.* Vaccine, 2008. **26**(25): p. 3112-20.
50. Rosati, M., et al., *Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation.* Vaccine, 2008. **26**(40): p. 5223-9.
51. Curcio, C., et al., *DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice.* Cancer Gene Ther., 2008. **15**(2): p. 108-114.
52. Ugen, K.E., et al., *Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation.* Cancer Gene Ther., 2006. **13**(10): p. 969-974.
53. Tebas, P., et al., *Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report.* N Engl J Med, 2017.
54. Tebas, P., et al., *Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers.* J Infect Dis, 2019.
55. De Rosa, S.C., et al., *Robust antibody and cellular responses induced by DNA-only vaccination for HIV.* JCI Insight, 2020. **5**(13).
56. Chandrashekar, A., et al., *SARS-CoV-2 infection protects against rechallenge in rhesus macaques.* Science, 2020.
57. Patel, A., et al., *Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model.* bioRxiv, 2020: p. 2020.07.28.225649.
58. European Commission, *Directorate-General: A Guideline on Summary of Product Characteristics (SmPC)*. 2009, EMA.
59. Diehl, M.C., et al., *Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers.* Hum Vaccin Immunother, 2013. **9**(10): p. 2246-52.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
	Bell's Palsy
	Transverse myelitis
	Narcolepsy
Hematologic	Thrombocytopenia
	Immune thrombocytopenia (ITP)
	Disseminated intravascular coagulation (DIC)
	Hemorrhagic stroke
	Non-hemorrhagic stroke
	Deep Vein Thrombosis (DVT)
	Pulmonary Embolism (PE)
Immunologic	Anaphylaxis
	Vasculitides
Cardiac	Acute cardiac failure
	Myocarditis/pericarditis
	Acute myocardial infarction
Other	Septic shock-like syndrome
	Appendicitis
	Multisystem Inflammatory Syndrome
	Acute kidney failure

Signature Page for VV-TMF-00448 v5.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 02-Apr-2021 23:46:56 GMT+0000

Signature Page for VV-TMF-00448 v5.0

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690

Protocol Version: 6.0

Protocol Version Date: 30-Apr-2021

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 5.0, dated 2-Apr-2021, to Version 6.0, dated 29-Apr-2021. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. Based upon the review of immunology data from Phase 2, the dose of INO-4800 for the Phase 3 segment of the study has been updated to 2.0 mg. Additional background information has been included to justify the dose selection and the advancement of the trial into the Phase 3 segment;
2. Possible benefits of the trial have been added;
3. It has been clarified that for subjects who are seropositive at Screening, a COVID-19 Assessment Visit is not required to be performed based on further positive SARS-CoV-2 tests during the trial;
4. The minimum fill volume of the SSC-0001 vials has been clarified to be 0.8mL.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 50 centers globally. Final country list to be determined.

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (SSC-0001) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0
Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0 mg) or placebo (SSC-0001). See Table 2 and Figure 1. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per U.S. Center for Disease Control (CDC) criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

Table 2: Phase 3 Segment

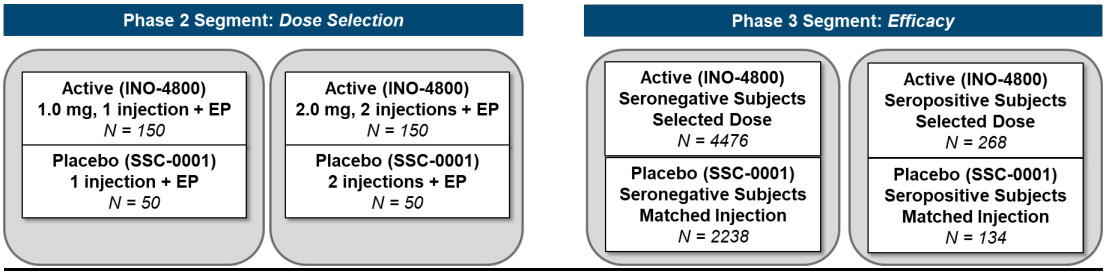
Treatment Arm	Sero status	Expected Number of Subjects	Approx. Expected Number of Subjects by Age Group		Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose of INO-4800 (mg)
			18-50	51+[a]					
INO-4800	Seroneg	4476	2238	2238	0, 28	2	1.0	2.0	4.0
	Seropos	268	134	134					
Placebo	Seroneg	2238	1119	1119	0, 28	2	0	0	0
	Seropos	134	67	67					
Total	**Seroneg**	6714	3357	3357					
	Seropos	402	201	201					
Total		7116							

[a]at least 711 subjects will be ≥65 years of age

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 3b. Antigen-specific cellular immune response such as measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding enzyme-linked immunosorbent assay (ELISA), pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot-forming assay (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (SSC-0001) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms per the case definition or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Phase 2 segment: Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Phase 3 segment: Subjects at high risk for SARS-CoV-2 exposure including subjects at high risk for severe COVID-19 who are 18 years and older.

Inclusion Criteria: Phase 2 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly

5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;
        iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria: Phase 3 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary

staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria: Phase 2 segment

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;

d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Exclusion Criteria: Phase 3 segment

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (this criterion only applies after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, after which this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
    - Current or anticipated use of disease modifying doses of systemic 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) or others;
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: Two 1.0mg ID injections of INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Placebo: Two ID injections of SSC-0001 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swabs)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltoid muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swabs and saliva specimens at COVID-19 assessment and convalescent visits. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, in the subject’s vehicle or at the subject’s home and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)[k]	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[l]	COVID-19 convalescent visit[m]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[n]	X[n]
Height and Weight	X																
HIV Serology		X															
Pregnancy Test[c]	X	X			X												
INO-4800 or Placebo + EP[d]		X			X												
Download EP Data[e]			X			X											
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[g]		X					X				X				X	X[r]	X
Humoral Samples[h]		X					X				X				X	X[r]	X
SARS-CoV-2 Serology[i]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Nasopharyngeal swabs)		X														X[o]	
Distribute Diary[p]			X			X											
Review/Collect Diary[q]				X	X		X										

a. Screening assessment occurs from -30 days to -1 day of Day 0. Screening and Day 0 visits may be combined if eligibility is able to be confirmed prior to dosing. If so, all assessments for Screening and Day 0 must be performed at the combined visit.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.

c. In women of childbearing potential. Urine pregnancy test at all indicated visits.
d. Intradermal injection(s) in skin preferably over deltoid region, or alternately over anterolateral quadriceps region, followed by EP at Day 0 and Day 28.
e. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
f. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
g. On Day 0, cellular sampling requires 64 mL of whole blood prior to 1st dose. At all other time points, collect 32 mL of whole blood. Cellular samples will be collected at selected clinical sites (estimated to include 711 subjects)
h. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce four serum aliquots of 2 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each.
i. SARS-CoV-2 antibody.
j. The Day 0 RT-PCR results will not be required prior to dosing on that day.
k. Day 42 visit must occur at least 10 days after Day 28 visit.
l. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or at a home visit and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
m. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization
n. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.
o. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
p. Diaries to be used at selected sites only (estimated to include 711 subjects).
q. Diary should be reviewed at the 14-day post-dose phone call or visit and collected at the next in-office visit.
r. When possible, cellular and humoral immunology samples will be collected. Cellular samples will be collected at selected sites only.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Given the continued number of cases globally, SARS-CoV-2 infections remain a serious unmet medical concern. Appropriate measures to prevent SARS-CoV-2 infections, including its variants, are not yet widely available.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [2-4]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [5, 6]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [7, 8], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [9].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [10], associated with substantial morbidity and mortality [11]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [12]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid

test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [4] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities

include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [9].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [9].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19, however there are several vaccines that are available under Emergency Use Authorization (EUA) in the United States and other countries. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of new strains of SARS-CoV-2, an effective prophylactic vaccine ideally induces immunity against not only SARS-CoV-2 Wuhan-Hu-

1 but also its variants. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for additional vaccines for prevention of SARS-CoV-2 infections.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 3 (REVEAL1) randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer (NCT03185013) and several Phase 2 trials for related and other indications and several Phase 2 trials for related and other indications. We have additionally built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV vaccine candidate was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [33].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [34-43]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [42, 44]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [45]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research

in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [46].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [47]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

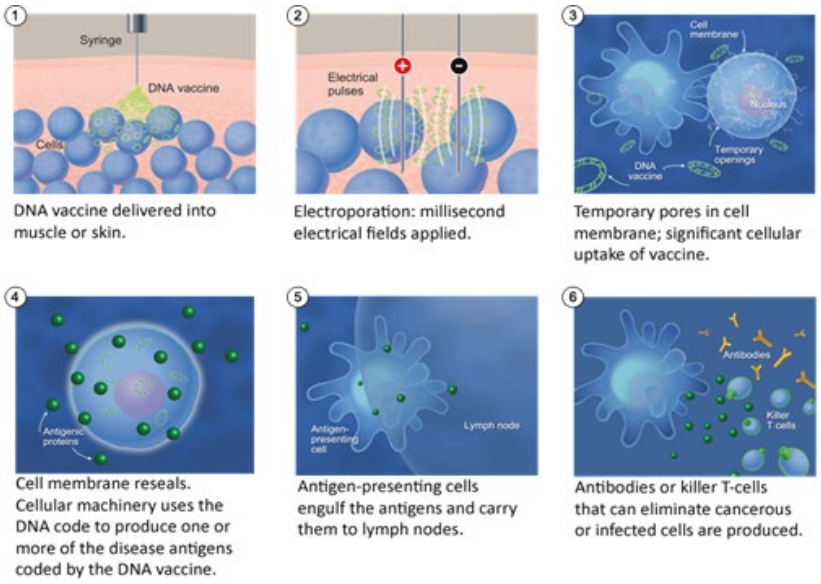
Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [48]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens for the activation of both cellular and humoral responses [49, 50]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [50]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [51, 52].

1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 Wuhan-Hu-1 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [53-55].

Following ID injection, the Inovio Pharmaceuticals' EP device [48] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES FOLLOWING VACCINATION WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [56]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [57].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11

adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of March 10, 2021, 35 related adverse events were reported cumulatively, of which all but three (Grade 2 injection site pruritus, lethargy and abdominal pain) were Grade 1 in severity.

Additional analyses showed that INO-4800 provides broad cross-reactive immune responses against variants of concern (VOC). Clinical samples, collected at varying timepoints post-immunization from subjects enrolled during Phase 1 INO-4800 clinical trial, were analyzed against the spike protein of different VOC (including UK variant B.1.1.7, South African variant B.1.351, and Brazilian variant P.1. strains) [58]. The results revealed neutralization activity against the P.1 variant (neutralizing antibodies levels comparable to those against wild-type) and reduced, but still measurable neutralization activity against the B.1.1.7 and B.1.351 variants. Additionally, it has been demonstrated that INO-4800 induces cross-reactive T cell responses against B.1.1.7, B.1.351, and P.1 variants that are comparable to the wild-type strain. Taken together, these data demonstrate that INO-4800 maintains cellular and/or humoral immune responses against the major SARS-CoV-2 variants that are currently in circulation, which will likely be critical factors necessary to impact the ongoing COVID-19 pandemic.

Please refer to the Investigator's Brochure, which will include future updates through the duration of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

This Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), to enable selection of a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >7000 subjects.

The safety and immunogenicity data from the Phase 2 segment strongly support the selection and advancement of the 2.0 mg dose of INO-4800 into the Phase 3 segment (see Section 1.3.7 for immunogenicity details). INO-4800's competitive safety/tolerability profile, nonclinical data supporting its potential to confer durable protection against severe

disease, ability to serve as a safe and tolerable homologous booster, and thermostability profile collectively support its potential as an additional tool for COVID-19 prevention with distinct advantages to facilitate global distribution and uptake.

1.3.6.1 Safety and tolerability of INO-4800

Safety and tolerability data collected on INO-4800 to date mirror the favorable safety profile of Inovio's plasmid DNA vaccines against multiple targets and indications. Nonclinical studies have revealed no safety concerns. Clinical studies (Phase 1 and Phase 2) have also not revealed any safety concerns as per reviews by independent Data Safety Monitoring Boards.

1.3.6.2 Nonclinical INO-4800 Data in Support of Potential Efficacy

The efficacy of INO-4800 in protecting against SARS-CoV-2 disease has been demonstrated in multiple nonclinical models. In the AAV6 human ACE2-transduced mouse model challenged with SARS-CoV-2, complete protection against lung virus load was observed [59]. Applying clinically relevant dosing and CELLECTRA-ID delivery parameters, INO-4800 has been tested in multiple nonhuman primate models, the gold standard large animal model for COVID-19 vaccine testing. We demonstrated protection against lung disease and viral load in the lower and upper respiratory tract in the rhesus macaque model after one or two doses of INO-4800 [60][61]. Furthermore, the durability of the impact of INO-4800 in reducing lung viral load was demonstrated in a rhesus macaque challenged with SARS-CoV-2 several months after immunization [57]. In conclusion, multiple nonclinical models have demonstrated the efficacy of INO-4800.

1.3.6.3 Potential Role of INO-4800 as a Booster

INO-4800 offers a potential role in serving as a booster to maintain protection against COVID-19 over time in the context of a potential endemic disease scenario. Unlike viral vectors, DNA elicits no anti-vector response and, therefore, can be repeatedly administered without a reduction in the generated immune responses. When subjects in the INO-4800 Phase 1 were provided a booster dose 6 to 10.5 months following the 2-dose regimen, there was no appreciable change in reactogenicity when compared to the first two doses, indicating that repeat dosing with INO-4800, as with other vaccines in Inovio's DNA platform, does not lead to an increase in reactogenicity. Inovio's DNA platform experience with Oncology DNA-vaccine targets have established that more than 10 sequential administrations of vaccine is capable of consistent re-boosting from an immunological perspective with no associated changes in safety and reactogenicity.

1.3.6.4 Thermostability of INO-4800

INO-4800 offers thermostability that could facilitate vaccine distribution globally. The current shelf life applied to INO-4800 clinical supplies is 24 months when stored at its recommended refrigerated storage condition of 5 ± 3°C. A 24-month real-time study for INO-4800 under refrigerated conditions (5°C) is ongoing; current Month 9 results are all within specification. Percent supercoiled forms, which is the strongest indication of DNA plasmid stability, decreased by only 2% (T0 97%, M9 95%) over the duration of the study to date, while percent total circular forms remained at 99%.

Inovio has a platform stability program with 12 different DNA plasmid products, all constructed with the same plasmid backbone and formulated in the same SSC buffer, at various DNA concentrations, and the stability data to date are all consistent with the excellent stability profile seen with INO-4800.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. Based on Inovio's extensive experience developing vaccine candidates against infectious diseases via the ID route ([54], [33]), a 2-dose regimen was considered to be optimal, based on the balanced humoral and cellular responses obtained 2 weeks post-dose 2, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In the Phase 2 segment of this trial, 1.0 mg and 2.0 mg of vaccine were administered by ID injection and followed immediately by EP at Day 0 and Day 28. The selection of the doses to test in Phase 2 is supported by the safety profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) in addition to our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial was to further evaluate the 1.0 mg and 2.0 mg doses of INO-4800 for each age group in order to select the optimal vaccination regimen in the Phase 3 efficacy segment. The final decision between the two doses by age group relies on safety and immunogenicity. The 1.0 mg and 2.0 mg doses in the Phase 1 study had a similar safety profile. The review of the Phase 2 data by the independent DSMB has not revealed any safety signals of concern. Furthermore, there were no differences in the safety profile between the 1.0 mg and 2.0 mg dosing groups to impact Phase 3 dose selection. However, the immunology data from the Phase 2 study revealed superior immunogenicity with the 2.0 mg dose over the 1.0 mg dose.

The immune response was measured using binding (ELISA) and neutralizing antibodies (pseudoneutralization) as well as cells capable of secreting IFN-gamma in a vaccine specific manner (ELISPOT). Data were analyzed for two age groups: ≥18 to ≤50 years of age and ≥51 years of age. The Phase 2 data illustrate that the 2.0 mg dose induced higher levels of SARS-CoV-2 spike specific antibodies as well as higher levels of IFN-gamma producing cells.

1.3.7.1 Binding Antibody Response

The binding antibody response was measured for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the geometric mean titer (GMT) for the 1.0 mg dose group was 123.3 at Day 0 compared to 938.8 at Week 6. The geometric mean fold rise was 7.8. The GMT for the 2.0 mg dose group was 93.5 at baseline compared to 2210.0 at Week 6. The geometric mean fold rise was 23.5.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 148.5 at Day 0 compared to 1182.1 at Week 6. The geometric mean fold rise in binding antibody titers was 7.9. The GMT for the 2.0 mg dose group was 99.5 at baseline compared to 2671.2 at Week 6. The geometric mean fold rise was 26.5.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 87.5 at Day 0 compared to 623.3 at Week 6. The geometric mean fold rise in titers was 7.6. The GMT for the 2.0 mg dose group was 84.0 at baseline compared to 1613.7 at Week 6. The geometric mean fold rise in binding antibodies was 19.2.

1.3.7.2 Neutralizing Antibody Response

The neutralizing antibody response was measured for all Phase 2 subjects at Days 0 and Week 6. Across all ages the geometric mean titer (GMT) for the 1.0 mg dose group was 32.2 at Day 0 compared to 93.6 at Week 6. The geometric mean fold rise in neutralizing

titers was 2.9. The GMT for the 2.0 mg dose group was 35.8 at baseline compared to 150.6 at Week 6. The geometric mean fold rise was 4.3.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 34.5 at Day 0 compared to 112.6 at Week 6. The geometric mean fold rise in neutralizing titers was 3.3. The GMT for the 2.0 mg dose group was 32.2 at baseline compared to 159.9 at week 6. The geometric mean fold rise was 5.0.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 28.4 at Day 0 compared to 67.4 at Week 6. The geometric mean fold rise in neutralizing titers was 2.3. The GMT for the 2.0 mg dose group was 43.3 at baseline compared to 135.7 at Week 6. The geometric mean fold rise was 3.2.

1.3.7.3 ELISPOT analysis

ELISPOT analysis was performed for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the median for the 1.0 mg dose group was 0 at Day 0 compared to 6.7 at Week 6. The median for the 2.0 mg dose group was 2.2 at baseline compared to 18.9 at Week 6. Subjects 18-50 years old in the 1.0 mg dose group had a median of that was 1.1 at Day 0 compared to 7.6 at Week 6. The median for the 2.0 mg dose group was 0.6 at baseline compared to 18.9 at Week 6. Subjects ≥51 years old in the 1.0 mg dose group had a median that was 0 at Day 0 compared to 10 at Week 6. The median for the 2.0 mg dose group was 3.3 at baseline compared to 18.4 at Week 6.

1.4 RISKS AND POTENTIAL BENEFITS

As of Dec 31, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile delineated in this section through the duration of the study.

1.4.1 POTENTIAL BENEFITS

As part of the trial, subjects will have access to COVID-19 diagnostic and antibody testing to which they might not otherwise have access. Additionally, subjects will have the benefit of contributing to research to help others in a time of a global pandemic. Benefits related to receipt of INO-4800 and protection from COVID-19 disease are unknown because the efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event

Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness
Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v4.0, dated 16-Nov-2020
[b] EU commission guideline on the SmPC September 2009 [62]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of Dec. 31, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction
- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of Dec. 31, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)
- Cardiac arrhythmias (product-related); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g., electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during

the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;

- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that “Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment” is an exclusion criterion (‘h’) in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 OVERALL BENEFIT/RISK CONCLUSION

While EUA vaccines are currently becoming available in many countries, the global availability to the general population remains limited. In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio’s DNA platform across all of its products, and INO-4800’s Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies the conduct of the Phase 2/3 trial.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses

to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo (SSC-0001). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0mg) or placebo (SSC-0001). Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥ 51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence of or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per CDC criteria [1], as listed below:

- Cancer
- Chronic kidney disease

- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease, that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for Phase 3, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS

	2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINTS

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 3b. Antigen-specific cellular immune response measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (SSC-0001) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the independent blinded EAC.

The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

*Local lab results will be accepted if the subject is hospitalized and a sample is not able to be obtained for analysis at central lab.

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:
  a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
  b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
  c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
  d. Significant acute renal, hepatic, or neurologic dysfunction,
  e. Admission to an ICU, or
  f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR SARS-COV-2 ASYMPTOMATIC INFECTION

Positive testing by SARS-CoV-2 serologic assay (performed at central lab);

- Without clinical signs or symptoms of COVID-19 disease since the previous negative serologic test.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

4.1.1 PHASE 2 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas

7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
10. Others, if approved by the medical monitor;

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 PHASE 3 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
   1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)

2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

4.2.1 PHASE 2 SEGMENT

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;

f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the prior 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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);
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;

n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.2.2 PHASE 3 SEGMENT

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:

   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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) or others;
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);

m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 0. mL or 0.8 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (SSC-0001): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 0.8 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by

needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.

- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [63].
- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles. The Pulse Generator and ID Applicator are reusable components. These components should be cleaned and disinfected prior to each subject's use according to the Cleaning and Maintenance procedure in the User Manual. The Pulse Generator and ID Applicator have been validated for up to 30 cleaning and disinfection cycles based on a maximum of 30 subjects being treated in a day. Therefore, the Pulse Generator and ID Applicator's use should be limited to 30 subjects in a day. Any potential risk of damage to the device due to cleaning and disinfection for more than 30 cycles has not been validated. Always inspect the device before use according to the instructions in the Maintenance section of the User Manual.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of SSC-0001 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Two 1.0mg ID injections of INO-4800 (~0.1mL dose volume) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)
- Placebo: Two ID injections of SSC-0001 (~0.1mL) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded throughout the trial. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

It is not deemed appropriate to unblind a subject's treatment assignment for the purpose of assisting the subject in making a decision regarding receipt a different COVID-19 vaccine (emergency use or licensed vaccine). Subjects should be advised that without efficacy data, INO-4800 has not been proven to be more protective than placebo in the prevention of COVID-19 and SARS-CoV-2 infection. Therefore, unblinding will not provide any meaningful information to inform a decision of receiving a different COVID-19 vaccine.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for such an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 or 0.8 mL. SSC-0001 is supplied in 2-mL vials at a minimum volume of 0.8 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or SSC-0001. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or SSC-0001 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration. Screening and Day 0 visits may be on the same day if eligibility is able to be confirmed prior to randomization. If so, all assessments for Screening and Day 0 must be performed at the combined visit.

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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics;
- Collect socio-behavioral assessment information (Section 6.4);
- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.6);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect urine for pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

<u>Phase 2 segment only:</u>

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.8).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or having occurred within 3 months prior to Screening. Subjects should be queried about any history of Hepatitis B, Hepatitis C and HIV.

In the Phase 3 segment, subjects with a self-reported history of Hepatitis B or C must provide documentation of liver enzymes that are not significantly elevated within the past 3 months. If such a report of liver enzyme testing is not available, this testing should be performed at Screening. Subjects with a history of Hepatitis C without cirrhosis who have completed treatment and have proof of an undetectable viral load at least 12 weeks following treatment may be enrolled and do not require liver enzymes within the past months.

Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 or an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

<u>Both Phase 2 and Phase 3 segments:</u>

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);

- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);
- Review restrictions for injection and EP (Section 6.4.7);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR (Day 0 only) (Section 6.4.8);
- Collect diary from Day 0 dose during Day 28 visit only(for selected sites only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data;
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide);
- Phase 2 segment: Distribute diary;
- Phase 3 segment, for selected sites: Distribute diary.

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);

Phase 2 segment only:
- Review diary (Section 6.4).

Phase 3 segment only:
- Review diary (for selected sites)(Section 6.4);

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;

- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5);

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect diary from Day 28 visit (for selected sites only);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.4 **Phone calls**

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:
- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.9);
- Record current concomitant medications/treatments (Section 6.4.6);

6.1.2.5 **Follow up clinic visits**

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 Day 201 visit only; Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine pregnancy test (Section 6.4);

Phase 2 segment:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5).

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or at a home visit and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR testing from the central lab. A local RT-PCR result will be considered acceptable in the case where a subject is hospitalized and a sample for central lab analysis is not able to be obtained, if it was obtained using. an assay performed by a laboratory accredited according to standards set by a national or regional accreditation body.

If a local lab is used to confirm the case, the report from the laboratory must be provided.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 only:

- Collect whole blood and serum for cellular and humoral immunology assessment, where possible (Phase 3 cellular immunology collection at selected sites only)(Section 6.5)
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (Section 6.4.8).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 2 segment only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial

personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a site code and a subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 assessment and convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

Blood samples will be collected at visits specified in the Schedule of Events (Tables 3 and 4). A total of approximately mL 245-330mL of blood will be drawn from each subject over the course of the study (inclusive of relevant safety and immunology samples at regular study visits per Tables 3 and 4). If the subjects is evaluated at COVID-19 visits, an additional volume of approximately 85-120mL will be collected. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening (Phase 2 segment only).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Pregnancy Testing:

Pregnancy testing will be performed on women of childbearing potential (WOCBP). All women will be assumed to be of childbearing potential unless they are:

- Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
- Women who are surgically sterile or have a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of a vasectomy, subjects should wait six (6) months post-vasectomy to be considered sterile.

Phase 2: For WOCBP, a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit.

Phase 3: For WOCBP, a urine pregnancy test will be obtained at Screening and will be performed immediately prior to any dosing.

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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol and at selected sites (estimated to include 711 subjects) in the Phase 3 segment. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with

the subject by the study staff during the next study phone call or visit and collected at the next in-person study visit. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be assessed.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin
3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of each injection site with CELLECTRA® 2000 at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections must be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection on different limbs and subsequently followed immediately by EP of the injection site with CELLECTRA® 2000 at Day 0 and Day 28.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

In Phase 2, samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and

SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. All subjects will be observed for 30 minutes following the IP administration procedure for immediate AEs. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

September 2007 "FDA Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 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) must be recorded on CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.7) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.7 RESTRICTIONS

In the Phase 2 segment of the trial, subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1.1). In the Phase 3 segment of the trial, subjects should refrain from becoming pregnant until receipt of the last dose of investigation product by using appropriate contraceptive measures (See Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature ≥38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine or any other drug/vaccine intended as COVID-19 prophylaxis during the trial. If a subject informs the site of their intent to receive another COVID-19 vaccine (emergency use or licensed vaccine), the subject should be informed that the safety and effectiveness of receiving INO-4800 followed by another COVID-19 vaccine has not been studied. In the Phase 3 segment, subjects should be reminded that if and when appropriate, the Sponsor would provide INO-4800 to those who received placebo in the trial.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.8 SARS-CoV-2 TESTING

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic or subject's vehicle or at the subject's home. During this visit, nasal swabs and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed. If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on nasopharyngeal specimens collected at Day 0. The Day 0 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

For subjects who are seronegative at baseline, if at any time during the trial, either the SARS-CoV-2 antibody or an RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or in the subject's home, nasopharyngeal swabs will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed on the sample(s) collected at the COVID-19 assessment visit.

6.4.9 COVID-19 DISEASE MONITORING

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of ≥ 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or in the subject's home.

Subjects with a confirmed COVID-19 diagnosis, per the case definition outlined in Section 3.7, prior to dose 2 or who have a positive SARS-CoV-2 PCR test at Day 0 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell, or with sequelae that appear to be permanent.

Subjects who require medical care for COVID-19 (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

6.5 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires 32 mL of whole blood be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood for cellular sampling and 8 mL serum for humoral sampling is required on Day 0 prior to 1st dose. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

Humoral samples will be collected on all subjects and cellular samples will be collected at selected sites (from approximately 711 subjects). Both humoral and cellular analysis will be conducted in the first 102 subjects age 18-50 and in the first 102 subjects age 51 and older enrolled at the sites that are selected for cellular sample collection. In addition, cellular and humoral samples will be analyzed on all subjects with COVID-19 when samples are available.

The immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene expression or flow cytometry, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;
- Confirmed COVID-19 disease.

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 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF;
- The Pregnancy outcomes of spontaneous abortion (miscarriage), ectopic pregnancy, fetal demise/stillbirth in a subject or subject partner following exposure to study treatment is considered to be 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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;
- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

The Investigator will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the Investigator'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 further administration of the investigational product in the clinical trial;
- Has accompanying or inducing symptoms or signs;
- Is judged by the Investigator 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The Investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment;
- Any Grade 4 AEs related to study treatment;
- Any report of anaphylaxis related to study treatment;
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

In the case of suspected Severe COVID-19 cases, the trial will be paused if a vaccine-to-placebo case split yields a relative risk with a 90% confidence interval lower bound >1. The minimum case split corresponding to this criterion is 8:0. In this scenario, the trial will pause until at least one additional case is accrued and the DSMB can review the data and make a recommendation regarding continued enrollment in the trial.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.
Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the Investigator until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 Investigator 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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

Investigators should use correct medical terminology/concepts when recording AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 Investigator will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with CTCAE.

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 Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs

and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator 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.

Investigators 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 Investigator 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 Investigator'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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the Investigator. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects in Phase 2 who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

Subjects in Phase 3 who are pregnant or expect to become pregnant prior to the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

The Investigator 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 dose administrations, must not be performed. The Investigator 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 Investigator if their partner becomes pregnant until study completion. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign a Pregnancy Information Collection Consent Form to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The site will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If an Investigator is contacted by the male subject or his pregnant partner, the Investigator 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed COVID-19 disease in subjects who are SARS-CoV-2 seronegative at baseline starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, and cases among baseline SARS-CoV-2 seropositive subjects. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern efficacy against variants, efficacy against asymptomatic infection, and binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% among baseline SARS-CoV-2 seronegative subjects will be tested with H_0: $p \geq .70/(.70+k)$ *vs*. H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population among those who are baseline SARS-CoV-2 seronegative will be primary for the analyses of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status of the subjects. Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

Among subjects who are SARS-CoV-2 seronegative at baseline, the primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.022 and the corresponding lower bound of the two-sided 95.6% CI for efficacy exceeds 30% (alpha-level adjusted for interim analyses, see Section 8.5.6), and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with

parameters (t, $p=\lambda_v/(\lambda_v+\lambda_c)$). The relationship between p and efficacy is: efficacy = (1-(1+k)p)/(1-p). Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but with 95% CIs and without the hypothesis test p-value.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects and by baseline SARS-CoV-2 serostatus.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint.. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

8.5.3 SAFETY ANALYSES

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3

segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.6 INTERIM ANALYSES

For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The two-sided type I error of 0.05 will not be adjusted for possible early stopping due to this aspect.

For the Phase 2 segment, group-level unblinded summaries of the immunogenicity and safety data will be produced once Week 6 visit immunology data and Week 8 visit safety data are complete for all subjects who have not discontinued, while maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all subjects who have not discontinued with remaining visits through the final visit. These summaries will allow the Sponsor to have results for the purposes of dose selection for the Phase 3 portion. No subject-level immunogenicity data will be produced, and subject-level immunogenicity data will not be available in the clinical trial database until all other clinical trial data are finalized at the end of the trial. No safety summary will be provided if the total number of subjects who experience the event of interest is greater than 0 and the count of the number of subjects with the event in a given treatment group relative to the total produces a percentage less than 3%, for a given summary. The group-level unblinded production of the summaries will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

For the Phase 3 segment, there are two planned formal interim efficacy analyses: one at 50% (75 cases) and one at 75% (112 cases) of the total required for the primary endpoint (149 cases). The Lan-DeMets O'Brien-Fleming approximate alpha-spending function will be used for the efficacy and futility boundaries. As such, the first interim analysis will utilize a one-sided nominal alpha of 0.0016, and the second interim analysis will utilize a one-sided nominal alpha of 0.0092. The final analysis will utilize a one-sided nominal alpha of 0.022. The DSMB will be responsible for the interim evaluations. The unblinded interim analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

If the prespecified criteria for efficacy above are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until 4500 subjects have 6 months of safety follow-up. At that point, the trial would be unblinded, and subjects who received placebo will be offered the active product.

8.5.7 MULTIPLICITY

There is one primary hypothesis that will be tested. As there are two interim analyses of the primary endpoint, the type I error rate will be controlled at two-sided 0.05 by using the Lan-DeMets O'Brien-Fleming approximate alpha-spending function (see Section 8.5.6).

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Efficacy

Phase 3 segment

The exploratory efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but with a 95% CI and without the hypothesis test p-value.

8.5.9.2 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline increases in antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean fold-rises and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.3 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 149 observed cases among baseline SARS-CoV-2 seronegative subjects will be required to provide 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60% and utilizing the methodology described in Section 8.5.1 and Section 8.5.6 . A sample size of 6714 baseline SARS-CoV-2 seronegative subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

Phase 3 Segment

Subjects will be randomized (2 INO-4800:1 Placebo). Randomization will be stratified according to two factors, each with two levels: a) age-group age category (18-50 years vs. ≥51 years) on Day 0, and b) presence or absence on Day 0 of underlying medical conditions that increase risk of severe COVID-19 disease, per US CDC criteria.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

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

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts

- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise

regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion.

If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
  - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
  - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor of this study. The Department of Defense, Joint Program Executive Office is providing funding for the Phase 2 segment of the study and

Inovio is providing funding for the Phase 3 segment. Clinical trial insurance has been taken out according to 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 per ICH E6 R1.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot-forming assay
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

16.0 REFERENCES

1. Centers for Disease Control and Prevention. *People with Certain Medical Conditions*. March 29, 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
2. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. **92**(4): p. 401-402.
3. Hui, D.S., et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.* Int J Infect Dis, 2020. **91**: p. 264-266.
4. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
5. GenBank. *Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome*. 2020; Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.
6. Smith, T.R.F., et al., *Immunogenicity of a DNA vaccine candidate for COVID-19.* Nat Commun, 2020. **11**(1): p. 2601.
7. World Health Organization, *Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance.* 2020.
8. World Health Organization, *Novel Coronavirus (2019-nCoV) Situation Report*. 2020.
9. Wiersinga, W.J., et al., *Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.* JAMA, 2020.
10. World Health Organization, *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. March 11, 2020.
11. Zou, L., et al., *SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.* N Engl J Med, 2020.
12. Center for Systems Science and Engineering at Johns Hopkins University, *COVID-19 Dashboard*. 2020.
13. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Intern Med, 2020.
14. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* Chin J Epidemiol, 2020. **41**(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
17. Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* Lancet, 2020. **395**(10223): p. 514-523.
18. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.* N Engl J Med, 2020. **382**(10): p. 970-971.
19. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020.* Euro Surveill, 2020. **25**(17).
20. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020. **26**(5): p. 672-675.

21. Liu, Y., et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus.* J Travel Med, 2020. **27**(2).
22. Centers for Disease Control and Prevention. *Symptoms of Coronavirus*. 2020 March 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
23. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* N Engl J Med, 2020.
24. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ, 2020. **369**: p. m1375.
25. Centers for Disease Control and Prevention. *COVID-19 Pandemic Planning Scenarios*. July 10, 2020 July 20, 2020 July 27, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
26. Lipsitch, M., et al., *Transmission dynamics and control of severe acute respiratory syndrome.* Science, 2003. **300**(5627): p. 1966-70.
27. Peiris, J.S., et al., *Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.* Lancet, 2003. **361**(9371): p. 1767-72.
28. Tsang, T.K., et al., *Influenza A Virus Shedding and Infectivity in Households.* J Infect Dis, 2015. **212**(9): p. 1420-8.
29. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
30. Long, Q.X., et al., *Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.* Nat Med, 2020.
31. Diao, B., et al., *Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19).* Front Immunol, 2020. **11**: p. 827.
32. Grifoni, A., et al., *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.* Cell, 2020. **181**(7): p. 1489-1501 e15.
33. Modjarrad, K., et al., *Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial.* Lancet Infect Dis, 2019. **19**(9): p. 1013-1022.
34. Suschak, J.J., J.A. Williams, and C.S. Schmaljohn, *Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity.* Hum Vaccin Immunother, 2017. **13**(12): p. 2837-2848.
35. Manickan, E., K.L. Karem, and B.T. Rouse, *DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology?* Crit Rev Immunol, 2017. **37**(2-6): p. 483-498.
36. Porter, K.R. and K. Raviprakash, *DNA Vaccine Delivery and Improved Immunogenicity.* Curr Issues Mol Biol, 2017. **22**: p. 129-138.
37. Li, L. and N. Petrovsky, *Molecular mechanisms for enhanced DNA vaccine immunogenicity.* Expert Rev Vaccines, 2016. **15**(3): p. 313-29.
38. Marc, M.A., E. Dominguez-Alvarez, and C. Gamazo, *Nucleic acid vaccination strategies against infectious diseases.* Expert Opin Drug Deliv, 2015. **12**(12): p. 1851-65.
39. Grunwald, T. and S. Ulbert, *Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases.* Clin Exp Vaccine Res, 2015. **4**(1): p. 1-10.
40. Tregoning, J.S. and E. Kinnear, *Using Plasmids as DNA Vaccines for Infectious Diseases.* Microbiol Spectr, 2014. **2**(6).
41. Williams, J.A., *Improving DNA vaccine performance through vector design.* Curr Gene Ther, 2014. **14**(3): p. 170-89.
42. Liu, M.A., *DNA vaccines: an historical perspective and view to the future.* Immunol Rev, 2011. **239**(1): p. 62-84.

43. Wahren, B. and M.A. Liu, *DNA Vaccines: Recent Developments and the Future.* Vaccines (Basel), 2014. **2**(4): p. 785-796wahren.
44. Ledgerwood, J.E. and B.S. Graham, *DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases.* Hum Vaccin, 2009. **5**(9): p. 623-6.
45. Keefer, M.C., et al., *Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network.* AIDS Res Hum Retroviruses, 1994. **10**(12): p. 1713-23.
46. Wu, F., et al., *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.* Medrxiv Preprint, 2020.
47. Martin, J.E., et al., *A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial.* Clin Vaccine Immunol, 2006. **13**(11): p. 1267-77.
48. Prud'homme, G.J., et al., *Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.* Curr Gene Ther, 2006. **6**(2): p. 243-73.
49. Hirao, L.A., et al., *Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques.* Vaccine, 2008. **26**(25): p. 3112-20.
50. Rosati, M., et al., *Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation.* Vaccine, 2008. **26**(40): p. 5223-9.
51. Curcio, C., et al., *DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice.* Cancer Gene Ther., 2008. **15**(2): p. 108-114.
52. Ugen, K.E., et al., *Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation.* Cancer Gene Ther., 2006. **13**(10): p. 969-974.
53. Tebas, P., et al., *Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report.* N Engl J Med, 2017.
54. Tebas, P., et al., *Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers.* J Infect Dis, 2019.
55. De Rosa, S.C., et al., *Robust antibody and cellular responses induced by DNA-only vaccination for HIV.* JCI Insight, 2020. **5**(13).
56. Chandrashekar, A., et al., *SARS-CoV-2 infection protects against rechallenge in rhesus macaques.* Science, 2020.
57. Patel, A., et al., *Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model.* bioRxiv, 2020: p. 2020.07.28.225649.
58. Andrade, V.M., et al., *INO-4800 DNA Vaccine Induces Neutralizing Antibodies and T cell Activity Against Global SARS-CoV-2 Variants.* bioRxiv, 2021: p. 2021.04.14.439719.
59. Gary E., W.B.M., Parzych E.M., Griffin B.D., Zhu X., Tailor N., Tursi N.J., Chan M., Purwar M., Vendramelli R., Choi J., Frost K.L, Reeder S., Liaw K., Tello E., Ali A.R., Yun K., Pei Y.,Thomas S.,Rghei A.D., Guilleman M.M., Muthumani K., Smith T., Wootton S.K., Patel A., Weiner D.B., Kobasa D., *A novel mouse AAV6 hACE2 transduction model of wild-type SARS-CoV-2 infection studied using synDNA immunogens.* iScience, 2021.
60. Gooch, K., et al., *One or two dose regimen of the SARS-CoV-2 synthetic DNA vaccine INO-4800 protects against respiratory tract disease burden in nonhuman primate challenge model.* Research Square 2021.
61. Trevor, S. *Development of INO-4800, a DNA-vaccine for COVID-19*. in *Keystone Symposia Antibodies and Vaccines as Drugs for COVID-19*. 2021.
62. European Commission, *Directorate-General: A Guideline on Summary of Product Characteristics (SmPC)*. 2009, EMA.

63. Diehl, M.C., et al., *Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers.* Hum Vaccin Immunother, 2013. **9**(10): p. 2246-52.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
	Bell's Palsy
	Transverse myelitis
	Narcolepsy
Hematologic	Thrombocytopenia
	Immune thrombocytopenia (ITP)
	Disseminated intravascular coagulation (DIC)
	Hemorrhagic stroke
	Non-hemorrhagic stroke
	Deep Vein Thrombosis (DVT)
	Pulmonary Embolism (PE)
Immunologic	Anaphylaxis
	Vasculitides
Cardiac	Acute cardiac failure
	Myocarditis/pericarditis
	Acute myocardial infarction
Other	Septic shock-like syndrome
	Appendicitis
	Multisystem Inflammatory Syndrome
	Acute kidney failure

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690
WHO UTN: U1111-1266-9952

Protocol Version: 7.0

Protocol Version Date: 8-Mar-2022

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]
[redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 6.0, dated 30-Apr-2021, to Version 7.0, dated 8-Mar-2022. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

1. The endpoint of prevention of all COVID-19 disease has been moved from primary to secondary, and the endpoint of prevention of severe COVID-19 disease has been moved from secondary to primary. This change has been made in response to information pertaining to the SARS-CoV-2 B.1.1.529 (Omicron) strain, which suggests that current vaccines (including INO-4800) targeting SARS-CoV-2 will not protect against acquisition of SARS-CoV-2 B.1.1.529 (Omicron) or symptomatic COVID-19 caused by B.1.1.529 (Omicron) but will protect against severe disease and hospitalization.
2. Based on the revision of the primary endpoint, the required number of cases of disease to meet the primary endpoint of severe COVID-19 disease and sample size have changed.
3. The interim analyses at 50% and 75% of cases have been removed. This is because the total number of cases of severe disease required to meet the primary endpoint is small, rendering any interim analysis of limited utility.
4. The primary analysis population has been clarified that it will include “subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline”.
5. All information previously clarified or corrected in protocol administrative memoranda and country-specific protocol amendments have been included in this amendment.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 70-100 centers in Latin America, Asia Pacific, North America and Africa.

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 10,002 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0
Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 10,002 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0 mg) or placebo. See Table 2 and Figure 1. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥51 years of age as is operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per U.S. Center for Disease Control (CDC) criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

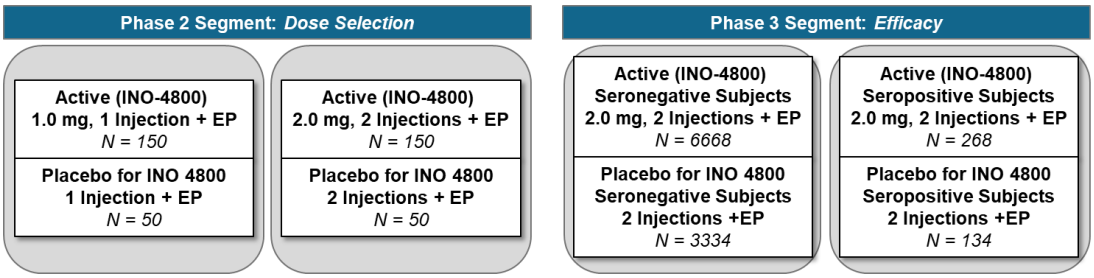
Table 2: Phase 3 Segment

Treatment Arm	Sero status	Expected Number of Subjects	Approx. Expected Number of Subjects by Age Group		Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose of INO-4800 (mg)
			18-50	51+					
INO-4800	Seroneg	6668	3334	3334	0, 28	2	1.0	2.0	4.0
	Seropos	268	134	134					
Placebo	Seroneg	3334	1667	1667	0, 28	2	0	0	0
	Seropos	134	67	67					
Total	**Seroneg**	10002	5001	5001					
	Seropos	402	201	201					
Total		10404							

This segment of the trial is case-driven. Among subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline, a total of 17 observed severe COVID-19 cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 90%. A sample size of 10,002 seronegative subjects is expected to be required to achieve the 17 severe cases assuming an underlying attack rate of 0.4%. The actual sample size may differ if the observed attack rate is different than projected. If the criteria for efficacy are met, placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed severe COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of severe COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	1. Incidence of virologically-confirmed severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs)

	1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	2a. Incidence of non-severe COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 3b. Antigen-specific cellular immune response such as measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4). Assays such as binding enzyme-linked immunosorbent assay (ELISA),

pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot-forming assay (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease (including severe disease) is suspected based on symptoms per the case definition or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC. The EAC will adjudicate all suspected COVID-19 events and determine whether cases meet the case definitions (per Section 3.7) for COVID-19 disease, severe COVID-19 or SARS-CoV-2 asymptomatic infection.

Clinical Trial Population:

Phase 2 segment: Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Phase 3 segment: Subjects at high risk for SARS-CoV-2 exposure including subjects at high risk for severe COVID-19 who are 18 years and older.

Inclusion Criteria: Phase 2 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)

4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;
        iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria: Phase 3 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:

1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      - **i.** hormonal contraception including implants, injections or oral;
      - **ii.** two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      - **iii.** intrauterine device or intrauterine system;
      - **iv.** abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria: Phase 2 segment

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;

c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;

- Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
- Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Exclusion Criteria: Phase 3 segment

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) within 72 hours prior to Day 0 dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (this criterion only applies after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, after which this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
    - Current or anticipated use of disease modifying doses of systemic 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) or others;
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;

- Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
- Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of Placebo (saline sodium citrate buffer or SSC) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: Two 1.0mg ID injections of INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Placebo: Two ID injections of Placebo followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days). Placebo may also be referred to as Placebo for INO-4800 or Sterile SSC Buffer.

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo for INO-4800 (sterile saline sodium citrate (SSC) buffer), refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swabs)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltoid muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swabs and saliva specimens at COVID-19 assessment and convalescent visits. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, in the subject’s vehicle or at the subject’s home and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)[k]	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[l]	COVID-19 convalescent visit[m]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[n]	X[n]
Height and Weight	X																
HIV Serology		X															
Pregnancy Test[c]	X	X			X												
INO-4800 or Placebo + EP[d]		X			X												
Download EP Data[e]			X			X											
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[g]		X					X				X				X	X[r]	X
Humoral Samples[h]		X					X				X				X	X[r]	X
SARS-CoV-2 Serology[i]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Nasopharyngeal swabs)		X[j]														X[o]	
Distribute Diary[p]			X			X											
Review/Collect Diary[q]				X	X		X										

a. Screening assessment occurs from -30 days to -1 day of Day 0. Screening and Day 0 visits may be combined if eligibility is able to be confirmed prior to dosing. If so, all assessments for Screening and Day 0 must be performed at the combined visit.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.

c. In women of childbearing potential. Urine pregnancy test at all indicated visits.
d. Intradermal injection(s) in skin preferably over deltoid region, or alternately over anterolateral quadriceps region, followed by EP at Day 0 and Day 28.
e. Following administration of INO-4800 or placebo, a subset of sites will be required to download EP data from the CELLECTRA® 2000 device and provided to Inovio.
f. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
g. On Day 0, cellular sampling requires 64 mL of whole blood prior to 1st dose. At all other time points, collect 32 mL of whole blood. Cellular samples will be collected at selected clinical sites (estimated to include 711 subjects)
h. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce four serum aliquots of 2 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each.
i. SARS-CoV-2 antibody. Screening samples will be tested in the clinic via rapid test to detect antibodies against the Spike protein. Samples collected pre-dose Day 0 and at subsequent timepoints will be tested at a study-designated lab to detect antibodies against the Nucleocapsid protein.
j. The Day 0 RT-PCR results will not be required prior to dosing on that day.
k. Day 42 visit must occur at least 10 days after Day 28 visit.
l. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or at a home visit and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
m. For subjects with virologically-confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of any specimen testing positive for SARS-CoV-2 RT-PCR. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization
n. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.
o. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
p. Diaries to be used at selected sites only (estimated to include 711 subjects).
q. Diary should be reviewed at the 14-day post-dose phone call or visit and collected at the next in-office visit.
r. When possible, cellular and humoral immunology samples will be collected. Cellular samples will be collected at selected sites only.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Given the continued number of cases globally, SARS-CoV-2 infections remain a serious unmet medical concern. Appropriate measures to prevent SARS-CoV-2 infections, including its variants, are not yet widely available.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [2-4]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [5, 6]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [7, 8], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [9].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [10], associated with substantial morbidity and mortality [11]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [12]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid

test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [4] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities

include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [9].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [9].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19, however there are several vaccines that are available under Emergency Use Authorization (EUA) in the United States and other countries. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of new strains of SARS-CoV-2, an effective prophylactic vaccine ideally induces immunity against not only SARS-CoV-2 Wuhan-Hu-

1 but also its variants. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for additional vaccines for prevention of SARS-CoV-2 infections.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 3 (REVEAL1) randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer (NCT03185013) and several Phase 2 trials for related and other indications and several Phase 2 trials for related and other indications. We have additionally built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV vaccine candidate was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [33].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [34-43]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [42, 44]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [45]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research

in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [46].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [47]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

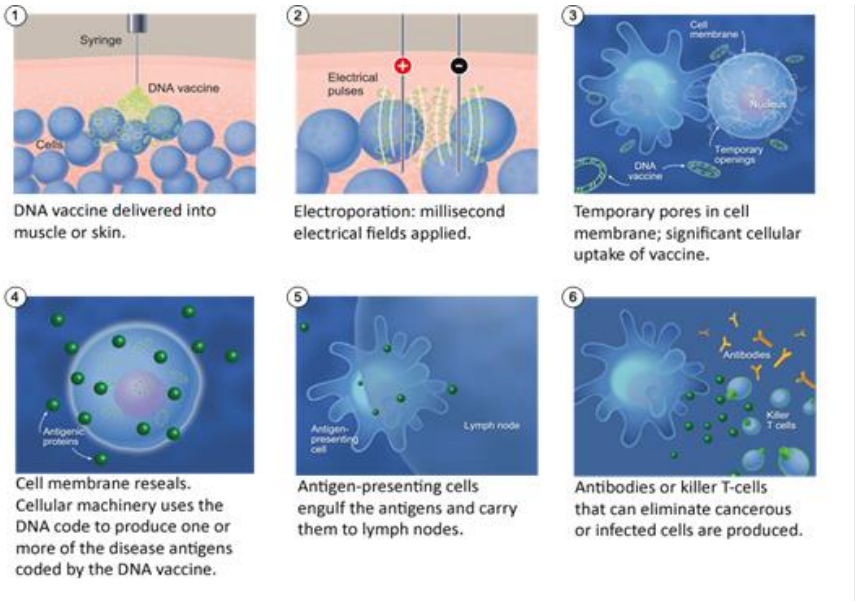
Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [48]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens for the activation of both cellular and humoral responses [49, 50]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [50]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [51, 52].

1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 Wuhan-Hu-1 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [53-55].

Following ID injection, the Inovio Pharmaceuticals' EP device [48] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES FOLLOWING VACCINATION WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [56]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [57].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11

adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of March 10, 2021, 35 related adverse events were reported cumulatively, of which all but three (Grade 2 injection site pruritus, lethargy and abdominal pain) were Grade 1 in severity.

Additional analyses showed that INO-4800 provides broad cross-reactive immune responses against variants of concern (VOC). Clinical samples, collected at varying timepoints post-immunization from subjects enrolled during Phase 1 INO-4800 clinical trial, were analyzed against the spike protein of different VOC (including UK variant B.1.1.7, South African variant B.1.351, and Brazilian variant P.1. strains) [58]. The results revealed neutralization activity against the P.1 variant (neutralizing antibodies levels comparable to those against wild-type) and reduced, but still measurable neutralization activity against the B.1.1.7 and B.1.351 variants. Additionally, it has been demonstrated that INO-4800 induces cross-reactive T cell responses against B.1.1.7, B.1.351, and P.1 variants that are comparable to the wild-type strain. Taken together, these data demonstrate that INO-4800 maintains cellular and/or humoral immune responses against the major SARS-CoV-2 variants that are currently in circulation, which will likely be critical factors necessary to impact the ongoing COVID-19 pandemic.

Please refer to the Investigator's Brochure, which will include future updates through the duration of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

This Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), to enable selection of a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >7000 subjects.

The safety and immunogenicity data from the Phase 2 segment strongly support the selection and advancement of the 2.0 mg dose of INO-4800 into the Phase 3 segment (see Section 1.3.7 for immunogenicity details). INO-4800's competitive safety/tolerability profile, nonclinical data supporting its potential to confer durable protection against severe

disease, ability to serve as a safe and tolerable homologous booster, and thermostability profile collectively support its potential as an additional tool for COVID-19 prevention with distinct advantages to facilitate global distribution and uptake.

1.3.6.1 Safety and tolerability of INO-4800

Safety and tolerability data collected on INO-4800 to date mirror the favorable safety profile of Inovio's plasmid DNA vaccines against multiple targets and indications. Nonclinical studies have revealed no safety concerns. Clinical studies (Phase 1 and Phase 2) have also not revealed any safety concerns as per reviews by independent Data Safety Monitoring Boards.

1.3.6.2 Nonclinical INO-4800 Data in Support of Potential Efficacy

The efficacy of INO-4800 in protecting against SARS-CoV-2 disease has been demonstrated in multiple nonclinical models. In the AAV6 human ACE2-transduced mouse model challenged with SARS-CoV-2, complete protection against lung virus load was observed [59]. Applying clinically relevant dosing and CELLECTRA-ID delivery parameters, INO-4800 has been tested in multiple nonhuman primate models, the gold standard large animal model for COVID-19 vaccine testing. We demonstrated protection against lung disease and viral load in the lower and upper respiratory tract in the rhesus macaque model after one or two doses of INO-4800 [60, 61]. Furthermore, the durability of the impact of INO-4800 in reducing lung viral load was demonstrated in a rhesus macaque challenged with SARS-CoV-2 several months after immunization [57]. In conclusion, multiple nonclinical models have demonstrated the efficacy of INO-4800.

1.3.6.3 Potential Role of INO-4800 as a Booster

INO-4800 offers a potential role in serving as a booster to maintain protection against COVID-19 over time in the context of a potential endemic disease scenario. Unlike viral vectors, DNA elicits no anti-vector response and, therefore, can be repeatedly administered without a reduction in the generated immune responses. When subjects in the INO-4800 Phase 1 were provided a booster dose 6 to 10.5 months following the 2-dose regimen, there was no appreciable change in reactogenicity when compared to the first two doses, indicating that repeat dosing with INO-4800, as with other vaccines in Inovio's DNA platform, does not lead to an increase in reactogenicity. Inovio's DNA platform experience with Oncology DNA-vaccine targets have established that more than 10 sequential administrations of vaccine is capable of consistent re-boosting from an immunological perspective with no associated changes in safety and reactogenicity.

1.3.6.4 Thermostability of INO-4800

INO-4800 offers thermostability that could facilitate vaccine distribution globally. The current shelf life applied to INO-4800 clinical supplies is 24 months when stored at its recommended refrigerated storage condition of 5 ± 3°C. A 24-month real-time study for INO-4800 under refrigerated conditions (5°C) is ongoing; current Month 9 results are all within specification. Percent supercoiled forms, which is the strongest indication of DNA plasmid stability, decreased by only 2% (T0 97%, M9 95%) over the duration of the study to date, while percent total circular forms remained at 99%.

Inovio has a platform stability program with 12 different DNA plasmid products, all constructed with the same plasmid backbone and formulated in the same SSC buffer, at various DNA concentrations, and the stability data to date are all consistent with the excellent stability profile seen with INO-4800.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. Based on Inovio's extensive experience developing vaccine candidates against infectious diseases via the ID route ([54], [33]), a 2-dose regimen was considered to be optimal, based on the balanced humoral and cellular responses obtained 2 weeks post-dose 2, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In the Phase 2 segment of this trial, 1.0 mg and 2.0 mg of vaccine were administered by ID injection and followed immediately by EP at Day 0 and Day 28. The selection of the doses to test in Phase 2 is supported by the safety profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) in addition to our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial was to further evaluate the 1.0 mg and 2.0 mg doses of INO-4800 for each age group in order to select the optimal vaccination regimen in the Phase 3 efficacy segment. The final decision between the two doses by age group relies on safety and immunogenicity. The 1.0 mg and 2.0 mg doses in the Phase 1 study had a similar safety profile. The review of the Phase 2 data by the independent DSMB has not revealed any safety signals of concern to date. Furthermore, there have not been substantial differences in the safety profile between the 1.0 mg and 2.0 mg dosing groups to impact Phase 3 dose selection. However, the interim immunology data from the Phase 2 study revealed superior immunogenicity with the 2.0 mg dose over the 1.0 mg dose. Data were analyzed for two age groups: ≥18 to ≤50 years of age and ≥51 years of age. The results illustrate that the 2.0 mg dose induced higher levels of SARS-CoV-2 spike specific antibodies as well as higher levels of IFN-gamma producing cells.

In November 2021, genotypic characterization identified a new VOC, Omicron, that has rapidly increased in prevalence. Omicron has acquired a large number of mutations, which not only gives it a growth advantage over the delta variant, but also allows it to evade the binding and neutralizing antibody responses generated by current COVID-19 vaccines or those of natural infection.

As with other COVID-19 vaccines[62], INO-4800 exhibited significantly decreased levels of both neutralizing and binding antibodies against Omicron, relative to other VOCs. However, in vitro assessment of INO-4800 against Omicron showed full maintenance of T cell responses, including CD8+ responses. The maintenance and preservation of T cell responses remains a consistent observation for INO-4800 against the ancestral virus and across all VOCs tested, including Delta and Omicron. T cell responses are thought to play an important role in protection against severe disease and death and may be central to the durability of vaccine protection[63].

The recognition of the importance of vaccine efficacy against severe disease is reflected in the January 2022 WHO Target Product Profiles for COVID-19 Vaccines. In light of this changing COVID-19 vaccine landscape and the maintenance of T cell responses against Omicron by INO-4800, Inovio Pharmaceuticals has amended the primary endpoint of this trial from "Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline" to "Incidence of virologically-confirmed severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (EOS) in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline".

1.3.7.1 Binding Antibody Response

The binding antibody response was measured for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the geometric mean titer (GMT) for the 1.0 mg dose group was 123.3 at Day 0 compared to 938.8 at Week 6. The geometric mean fold rise was 7.8. The GMT for the 2.0 mg dose group was 93.5 at baseline compared to 2210.0 at Week 6. The geometric mean fold rise was 23.5.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 148.5 at Day 0 compared to 1182.1 at Week 6. The geometric mean fold rise in binding antibody titers was 7.9. The GMT for the 2.0 mg dose group was 99.5 at baseline compared to 2671.2 at Week 6. The geometric mean fold rise was 26.5.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 87.5 at Day 0 compared to 623.3 at Week 6. The geometric mean fold rise in titers was 7.6. The GMT for the 2.0 mg dose group was 84.0 at baseline compared to 1613.7 at Week 6. The geometric mean fold rise in binding antibodies was 19.2.

1.3.7.2 Neutralizing Antibody Response

The neutralizing antibody response was measured for all Phase 2 subjects at Days 0 and Week 6. Across all ages the geometric mean titer (GMT) for the 1.0 mg dose group was 32.2 at Day 0 compared to 93.6 at Week 6. The geometric mean fold rise in neutralizing titers was 2.9. The GMT for the 2.0 mg dose group was 35.8 at baseline compared to 150.6 at Week 6. The geometric mean fold rise was 4.3.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 34.5 at Day 0 compared to 112.6 at Week 6. The geometric mean fold rise in neutralizing titers was 3.3. The GMT for the 2.0 mg dose group was 32.2 at baseline compared to 159.9 at week 6. The geometric mean fold rise was 5.0.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 28.4 at Day 0 compared to 67.4 at Week 6. The geometric mean fold rise in neutralizing titers was 2.3. The GMT for the 2.0 mg dose group was 43.3 at baseline compared to 135.7 at Week 6. The geometric mean fold rise was 3.2.

1.3.7.3 ELISPOT analysis

ELISPOT analysis was performed for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the median for the 1.0 mg dose group was 0 at Day 0 compared to 6.7 at Week 6. The median for the 2.0 mg dose group was 2.2 at baseline compared to 18.9 at Week 6. Subjects 18-50 years old in the 1.0 mg dose group had a median of 1.1 at Day 0 compared to 7.6 at Week 6. The median for the 2.0 mg dose group was 0.6 at baseline compared to 18.9 at Week 6. Subjects ≥51 years old in the 1.0 mg dose group had a median that was 0 at Day 0 compared to 10 at Week 6. The median for the 2.0 mg dose group was 3.3 at baseline compared to 18.4 at Week 6.

1.4 RISKS AND POTENTIAL BENEFITS

As of Dec 31, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile delineated in this section through the duration of the study.

1.4.1 POTENTIAL BENEFITS

As part of the trial, subjects will have access to COVID-19 diagnostic and antibody testing to which they might not otherwise have access. Additionally, subjects will have the benefit of contributing to research to help others in a time of a global pandemic. Benefits related to receipt of INO-4800 and protection from COVID-19 disease are unknown because the efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness
Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v4.0, dated 16-Nov-2020
[b] EU commission guideline on the SmPC September 2009 [64]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of Dec. 31, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction
- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of Dec. 31, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior

vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)

- Cardiac arrhythmias (product-related); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that “ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)” is an exclusion criterion (‘j’) in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g., electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;
- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that “Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for

worsening disease during the 6 weeks prior to enrollment" is an exclusion criterion ('h') in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 Overall Benefit/Risk Conclusion

While EUA vaccines are currently becoming available in many countries, the global availability to the general population remains limited. In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio's DNA platform across all of its products, and INO-4800's Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies the conduct of the Phase 2/3 trial.

2.0 Objectives and Purpose

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 Hypothesis

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed severe COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 Clinical Trial Design and Endpoints

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 10,002 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 10,002 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0mg) or placebo. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥ 51 years of age as is operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence of or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per CDC criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease, that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

This segment of the trial is case-driven. Among subjects who are seronegative and RT-PCR negative at baseline, a total of 17 observed severe cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 90%. A sample size of 10,002 seronegative subjects is expected to be required to achieve the 17 severe cases assuming an underlying attack rate of 0.4%. The actual sample size may differ if the observed attack rate is different than projected. If the criteria for efficacy are met, placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for Phase 3, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of severe COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	1. Incidence of virologically-confirmed severe COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	2a. Incidence of non-severe COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID- in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINTS

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2	2. Incidence of SARS-CoV-2 asymptomatic infections in in subjects who are SARS-CoV-2

asymptomatic infection in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline	seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 3b. Antigen-specific cellular immune response measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease (including severe COVID-19) is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the independent blinded EAC. The EAC will adjudicate all suspected COVID-19 events and determine whether cases meet the case definitions for COVID-19 disease, severe COVID-19 or SARS-CoV-2 asymptomatic infection.

The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

*Local lab results will be accepted if the subject is hospitalized and a sample is not able to be obtained for analysis at central lab.

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:

a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
d. Significant acute renal, hepatic, or neurologic dysfunction,
e. Admission to an ICU, or
f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR SARS-COV-2 ASYMPTOMATIC INFECTION

Positive testing by SARS-CoV-2 serologic assay detecting antibodies to the Nucleocapsid protein.

- Without clinical signs or symptoms of COVID-19 disease since the previous negative serologic test.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4). Assays such as binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

4.1.1 PHASE 2 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;

c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
    9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
    10. Others, if approved by the medical monitor;
f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        - hormonal contraception including implants, injections or oral;
        - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        - intrauterine device or intrauterine system;
        - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 PHASE 3 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
    2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
    4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
    7. Person 51 years or older living in a multigenerational (at least 3 generations) household
    8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
    9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
    10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.
f. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;

iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

4.2.1 PHASE 2 SEGMENT

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the prior 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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);

- History of solid organ or bone marrow transplantation;
- History of or current receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.2.2 PHASE 3 SEGMENT

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) within 72 hours prior to Day 0 dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:

   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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) or others;

- History of solid organ or bone marrow transplantation;
- History of or current receipt of any other clinically significant immunosuppressive drugs
- Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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.

If HIV testing performed at Day 0, in the setting of no prior HIV diagnosis, returns with a positive result after the subject has already received the Day 0 dose, the subject should be discontinued from further dosing and followed for safety.

The Investigator must notify the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

If a subject receives a non-study COVID-19 vaccine either authorized under emergency use or licensed, during the trial, the subject should provide details of the vaccine to study staff and the Investigator should enter the details as a concomitant medication. The subject should be advised that there is inadequate information regarding the safety and effectiveness of other COVID-19 vaccines when received following the receipt of INO-4800. Furthermore, the subject should be requested to remain in the trial (according to the Schedule of Events outlined in Tables 3 and 4).

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where

the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo: Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL, 0.8 mL, or 1.5 mL will be filled into 2R glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo: Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 0.8 mL or 1.5 mL in 2R glass vials, stoppered, and sealed with aluminum caps. Placebo may also be referred to as Placebo for INO-4800 or Sterile SSC Buffer.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.
- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study

evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [65].

- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles. The Pulse Generator and ID Applicator are reusable components. These components should be cleaned and disinfected prior to each subject's use according to the Cleaning and Maintenance procedure in the User Manual. The Pulse Generator and ID Applicator have been validated for up to 30 cleaning and disinfection cycles based on a maximum of 30 subjects being treated in a day. Therefore, the Pulse Generator and ID Applicator's use should be limited to 30 subjects in a day. Any potential risk of damage to the device due to cleaning and disinfection for more than 30 cycles has not been validated. Always inspect the device before use according to the instructions in the Maintenance section of the User Manual.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of placebo (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Two 1.0mg ID injections of INO-4800 (~0.1mL dose volume) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)
- Placebo: Two ID injections of placebo (~0.1mL) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

It is not deemed appropriate to unblind a subject's treatment assignment for the purpose of assisting the subject in making a decision regarding receipt a different COVID-19 vaccine (emergency use or licensed vaccine). Subjects may be advised that without efficacy data, INO-4800 has not been proven to be more protective than placebo in the prevention of COVID-19 and SARS-CoV-2 infection. Therefore, unblinding will not provide any meaningful information to inform a decision of receiving a different COVID-19 vaccine.

The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for such an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

The Phase 2 segment of the trial will be unblinded following subjects reaching the Week 30 visit.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. Placebo is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 or 0.8 mL. Placebo is supplied in 2-mL vials at a minimum volume of 0.8 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or placebo. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or placebo into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration. Screening and Day 0 visits may be on the same day if eligibility is able to be confirmed prior to randomization. If so, all assessments for Screening and Day 0 must be performed at the combined visit.

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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics;
- Collect socio-behavioral assessment information (Section 6.4);
- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.6);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect urine for pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.8).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or having occurred within 3 months prior to Screening. Subjects should be queried about any history of Hepatitis B, Hepatitis C and HIV.

In the Phase 3 segment, subjects with a self-reported history of Hepatitis B or C must provide documentation of liver enzymes that are not significantly elevated within the past 3 months. If such a report of liver enzyme testing is not available, this testing should be performed at Screening. Subjects with a history of Hepatitis C without cirrhosis who have completed treatment and have proof of an undetectable viral load at least 12 weeks following treatment may be enrolled and do not require liver enzymes within the past months.

Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 or an undetectable viral load within the

past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);
- Review restrictions for injection and EP (Section 6.4.7);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR (Day 0 only) (Section 6.4.8);
- Collect diary from Day 0 dose during Day 28 visit only (for selected sites only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data (for selected sites only);
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide);
- Phase 2 segment: Distribute diary;
- Phase 3 segment, for selected sites: Distribute diary.

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);

Phase 2 segment only:
- Review diary (Section 6.4).

Phase 3 segment only:
- Review diary (for selected sites)(Section 6.4);

6.1.2.3 Day 42 Visit

The Day 42 visit must occur at least 10 days after Day 28 visit.

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5);

Phase 2 segment only:
- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect diary from Day 28 visit (for selected sites only);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.9);
- Record current concomitant medications/treatments (Section 6.4.6);

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 Day 201 visit only; Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 segment:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);

- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect urine pregnancy test (Section 6.4).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5).

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or at a home visit and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR testing from the central lab. A local RT-PCR result will be considered acceptable in the case where a subject is hospitalized and a sample for central lab analysis is not able to be obtained, if it was obtained using. an assay performed by a laboratory accredited according to standards set by a national or regional accreditation body.

If a local lab is used to confirm the case, the report from the laboratory must be provided.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 only:

- Collect whole blood and serum for cellular and humoral immunology assessment, where possible (Phase 3 cellular immunology collection at selected sites only) (Section 6.5)
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (Section 6.4.8).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with virologically confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of any specimen testing positive for SARS-CoV-2 RT-PCR. If acute symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment where possible (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 2 segment only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;
- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a site code and a subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make

them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 assessment and convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

Blood samples will be collected at visits specified in the Schedule of Events (Tables 3 and 4). A total of approximately mL 245-330mL of blood will be drawn from each subject over the course of the study (inclusive of relevant safety and immunology samples at regular study visits per Tables 3 and 4). If the subject is evaluated at COVID-19 visits, an additional volume of approximately 85-120mL will be collected. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening (Phase 2 segment only).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be performed at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening in the clinic using a rapid test which detects Spike protein antibodies and at pre-dose Day 0 and subsequent visits via testing at a study-designated lab which detects antibodies to Nucleocapsid protein. Timepoints are specified in the Schedule of Events (Tables 3 and 4).

Pregnancy Testing:

Pregnancy testing will be performed on women of childbearing potential (WOCBP). All women will be assumed to be of childbearing potential unless they are:

- Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
- Women who are surgically sterile or have a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of a vasectomy, subjects should wait six (6) months post-vasectomy to be considered sterile.

Phase 2: For WOCBP, a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit.

Phase 3: For WOCBP, a urine pregnancy test will be obtained at Screening and will be performed immediately prior to any dosing.

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 subject is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol and at selected sites (estimated to include 711 subjects) in the Phase 3 segment. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the next study phone call or visit and collected at the next in-person study visit. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be assessed.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September

2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin
3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of each injection site with CELLECTRA® 2000 at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections must be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection on different limbs and subsequently followed immediately by EP of the injection site with CELLECTRA® 2000 at Day 0 and Day 28.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

In Phase 2, samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. All subjects will be observed for 30

minutes following the IP administration procedure for immediate AEs. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

September 2007 "FDA Guidance for Industry-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription), including receipt of any non-study COVID-19 vaccine (authorized under emergency use or licensed) received between informed consent and study discharge (see Section 4.2) must be recorded on the CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.7) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.7 RESTRICTIONS

In the Phase 2 segment of the trial, subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate

contraceptive measures (see Section 4.1.1). In the Phase 3 segment of the trial, subjects should refrain from becoming pregnant until receipt of the last dose of investigation product by using appropriate contraceptive measures (See Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature ≥38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine during the trial. In the Phase 3 segment, subjects should not receive any other drug/vaccine intended as COVID-19 prophylaxis during the trial.

For subjects in the Phase 2 segment of the trial, the receipt of any non-study prophylactic COVID-19 vaccine (authorized under emergency use or licensed) is no longer restricted, based upon increasing availability of EUA vaccine and completion of the Phase 2 data for purposes of Phase 3 dose selection.

If a subject informs the site of their intent to receive a non-study prophylactic COVID-19 vaccine (available either under emergency use or when licensed), the subject should be informed that the safety and effectiveness of receiving INO-4800 followed by receipt of another COVID-19 vaccine has not been studied.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.8 SARS-CoV-2 Testing

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic or subject's vehicle or at the subject's home. During this visit, nasal swabs and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed. If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing for Spike protein antibodies will be performed via rapid test in the clinic during screening to identify previous SARS-CoV-2 infection. Serum samples will be collected prior to dosing at Day 0 and at each subsequent visit (see Table 4: Schedule of Events) and tested for nucleoprotein antibodies at the study-designated lab to identify any intervening SARS-CoV-2 infection that may occur, regardless of symptoms, between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on nasopharyngeal specimens collected at Day 0. The Day 0 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

A subject should be evaluated at a COVID-19 assessment visit if:

- The SARS-CoV-2 serum antibody test by the study-designated lab (Nucleocapsid protein antibody assay) result becomes positive in subjects who tested seronegative at Day 0 (nucleoprotein antibody assay), with the exception of subjects who have a positive SARS-CoV-2 RT-PCR test result pre-dose on Day 0, or
- A SARS-CoV-2 RT-PCR test result or results of any local rapid testing outside of the study are positive any time after the subject receives the first dose at Day 0, or
- The subject has symptoms of COVID-19 (see Section 6.4.9).

During that COVID-19 Assessment Visit, which may be conducted in the clinic, from the subject's vehicle, or in the subject's home, nasopharyngeal swabs will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed on the sample(s) collected at the COVID-19 assessment visit.

6.4.9 COVID-19 DISEASE MONITORING

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of ≥ 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or in the subject's home.

Subjects with a confirmed COVID-19 diagnosis, per the case definition outlined in Section 3.7, prior to dose 2 or who have a positive SARS-CoV-2 PCR test at Day 0 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. If a subject is due for Dose 2 but SARS-CoV-2 RT-PCR results are not yet available from either Day 0 or a Suspected COVID-19 Assessment Visit, they should be dosed on schedule as long as they are currently asymptomatic.

Subjects with virologically confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of any specimen testing positive for SARS-CoV-2 RT-PCR. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell, or with sequelae that appear to be permanent.

Subjects who require medical care for COVID-19 (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be

provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

6.5 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires 32 mL of whole blood be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood for cellular sampling and 8 mL serum for humoral sampling is required on Day 0 prior to 1st dose. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

Humoral samples will be collected on all subjects and cellular samples will be collected at selected sites (from approximately 711 subjects). Both humoral and cellular analysis will be conducted in the first 102 subjects age 18-50 and in the first 102 subjects age 51 and older enrolled at the sites that are selected for cellular sample collection. In addition, cellular and humoral samples will be analyzed on all subjects with COVID-19 when samples are available.

The immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene expression or flow cytometry, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;
- Confirmed COVID-19 disease.

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 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF;
- The Pregnancy outcomes of spontaneous abortion (miscarriage), ectopic pregnancy, fetal demise/stillbirth in a subject or subject partner following exposure to study treatment is considered to be 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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;
- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

The Investigator will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the Investigator'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 further administration of the investigational product in the clinical trial;
- Has accompanying or inducing symptoms or signs;
- Is judged by the Investigator 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The Investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment (i.e., IP and/or the study device);
- Any Grade 4 AEs related to study treatment (i.e., IP and/or the study device);
- Any report of anaphylaxis related to study treatment (i.e., IP and/or the study device);
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee (SRC), who will determine whether dosing should be temporarily halted until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the SRC and/or a consultation with the DSMB Chair. If such a consultation occurs, the DSMB Chair and/or the SRC Chair may decide to convene an ad hoc meeting of the DSMB. Following such a meeting, the DSMB chair will render any recommendations to the SRC Chair. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will make a final decision regarding continuation of trial dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

In the case of suspected Severe COVID-19 cases, the trial will be paused if a vaccine-to-placebo case split yields a relative risk with a 90% confidence interval lower bound >1. The minimum case split corresponding to this criterion is 8:0. In this scenario, the trial will pause until at least one additional case is accrued and the DSMB can review the data and make a recommendation regarding continued enrollment in the trial.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE CRF Form and submitted to the Sponsor via EDC within 24 hours of becoming aware of the event. In the event the EDC is unavailable, the SAE/AESI Report Form (paper) should be used and submitted to the Sponsor within 24 hours of becoming aware of the event. In that case, the SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.

Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the Investigator until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 Investigator 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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

Investigators should use correct medical terminology/concepts when recording AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 Investigator will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with CTCAE.

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 Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator 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.

Investigators 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 Investigator 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 Investigator'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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the Investigator. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects in Phase 2 who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

Subjects in Phase 3 who are pregnant or expect to become pregnant prior to the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy CRF Form will be completed by the site in EDC and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. In the event the EDC is unavailable, the Pregnancy and Pregnancy Outcome Report Form (paper) should be used and submitted to the Sponsor within 24 hours of becoming aware of the pregnancy.

The Investigator 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 dose administrations, must not be performed. The Investigator 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 Investigator if their partner becomes pregnant until study completion. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign a Pregnancy Information Collection Consent Form to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The site will update the

Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If an Investigator is contacted by the male subject or his pregnant partner, the Investigator 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including malfunctions of the device (e.g. significant device malfunction causing injury or resulting in a hazard which could cause injury to the subject or user), 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. The Sponsor will review these reports for potential hazards that could cause an SAE. If Inovio determines that the malfunction could cause an SAE, the Inovio Medical Monitor will decide whether the Chair of the Safety Review Committee should be notified in accordance with Section 7.8.4.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed severe COVID-19 disease in subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, all cases, cases resulting in death, and cases among baseline SARS-CoV-2 seropositive subjects. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern efficacy against variants, efficacy against asymptomatic infection, and binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% among baseline SARS-CoV-2 seronegative and RT-PCR negative subjects will be tested with H_0: $p \geq .70/(.70+k)$ *vs.* H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with severe disease who receive INO-4800 relative to the total number of subjects with severe disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population among those who are baseline SARS-CoV-2 seronegative and RT-PCR negative will be primary for the analyses of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects. Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380

days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

Among subjects who are SARS-CoV-2 seronegative and RT-PCR negative at baseline, the primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with severe disease who receive INO-4800 relative to the total number of subjects with severe disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.025 and the corresponding lower bound of the two-sided 95% CI for efficacy exceeds 30%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-value.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects and by baseline SARS-CoV-2 serostatus.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

8.5.3 SAFETY ANALYSES

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to the Phase of the trial. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.6 INTERIM ANALYSES

For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The two-sided type I error of 0.05 will not be adjusted for possible early stopping due to this aspect.

For the Phase 2 segment, group-level unblinded summaries of the immunogenicity and safety data will be produced once Week 6 visit immunology data and Week 8 visit safety data are complete for all subjects who have not discontinued, while maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all subjects who have not discontinued with remaining visits through the final visit. These summaries will allow the Sponsor to have results for the purposes of dose selection for the Phase 3 portion. No subject-level immunogenicity data will be produced, and subject-level immunogenicity data will not be available in the clinical trial database until all other clinical trial data are finalized at the end of the trial. No safety summary will be provided if the total number of subjects who experience the event of interest is greater than 0 and the count of the number of subjects with the event in a given treatment group relative to the

total produces a percentage less than 3%, for a given summary. The group-level unblinded production of the summaries will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

8.5.7 MULTIPLICITY

Not applicable; there is one primary hypothesis that will be tested.

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Efficacy

Phase 3 segment

The exploratory efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but without the hypothesis test p-value.

8.5.9.2 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline increases in antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean fold-rises and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.3 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 17 observed severe cases among baseline SARS-CoV-2 seronegative and RT-PCR negative subjects will be required to provide 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 90% and utilizing the methodology described in Section 8.5.1. A sample size of 10,002 baseline SARS-CoV-2 seronegative subjects is expected to be required to achieve this number of cases assuming an underlying attack rate of approximately 0.4%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment

Subjects will be randomized (2 INO-4800:1 Placebo). Randomization will be stratified according to two factors, each with two levels: a) age-group age category (18-50 years vs. ≥51 years) on Day 0, and b) presence or absence on Day 0 of underlying medical conditions that increase risk of severe COVID-19 disease, per US CDC criteria.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes

(e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

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

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses

- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion.

If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
    - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.

- Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
- Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
- Assure that the trial facilities, including the pharmacy, continue to be acceptable.
- Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor of this study. The Department of Defense, Joint Program Executive Office is providing funding for the Phase 2 segment of the study and Inovio is providing funding for the Phase 3 segment. Clinical trial insurance has been taken out according to 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 per ICH E6 R1.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot-forming assay
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

16.0 REFERENCES

1. Centers for Disease Control and Prevention. *People with Certain Medical Conditions*. March 29, 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
2. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. **92**(4): p. 401-402.
3. Hui, D.S., et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.* Int J Infect Dis, 2020. **91**: p. 264-266.
4. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
5. GenBank. *Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome*. 2020; Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.
6. Smith, T.R.F., et al., *Immunogenicity of a DNA vaccine candidate for COVID-19.* Nat Commun, 2020. **11**(1): p. 2601.
7. World Health Organization, *Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance.* 2020.
8. World Health Organization, *Novel Coronavirus (2019-nCoV) Situation Report*. 2020.
9. Wiersinga, W.J., et al., *Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.* JAMA, 2020.
10. World Health Organization, *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. March 11, 2020.
11. Zou, L., et al., *SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.* N Engl J Med, 2020.
12. Center for Systems Science and Engineering at Johns Hopkins University, *COVID-19 Dashboard*. 2020.
13. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Intern Med, 2020.
14. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* Chin J Epidemiol, 2020. **41**(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
17. Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* Lancet, 2020. **395**(10223): p. 514-523.
18. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.* N Engl J Med, 2020. **382**(10): p. 970-971.
19. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020.* Euro Surveill, 2020. **25**(17).
20. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020. **26**(5): p. 672-675.

21. Liu, Y., et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus.* J Travel Med, 2020. **27**(2).
22. Centers for Disease Control and Prevention. *Symptoms of Coronavirus*. 2020 March 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
23. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* N Engl J Med, 2020.
24. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ, 2020. **369**: p. m1375.
25. Centers for Disease Control and Prevention. *COVID-19 Pandemic Planning Scenarios*. July 10, 2020 July 20, 2020 July 27, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
26. Lipsitch, M., et al., *Transmission dynamics and control of severe acute respiratory syndrome.* Science, 2003. **300**(5627): p. 1966-70.
27. Peiris, J.S., et al., *Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.* Lancet, 2003. **361**(9371): p. 1767-72.
28. Tsang, T.K., et al., *Influenza A Virus Shedding and Infectivity in Households.* J Infect Dis, 2015. **212**(9): p. 1420-8.
29. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
30. Long, Q.X., et al., *Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.* Nat Med, 2020.
31. Diao, B., et al., *Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19).* Front Immunol, 2020. **11**: p. 827.
32. Grifoni, A., et al., *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.* Cell, 2020. **181**(7): p. 1489-1501 e15.
33. Modjarrad, K., et al., *Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial.* Lancet Infect Dis, 2019. **19**(9): p. 1013-1022.
34. Suschak, J.J., J.A. Williams, and C.S. Schmaljohn, *Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity.* Hum Vaccin Immunother, 2017. **13**(12): p. 2837-2848.
35. Manickan, E., K.L. Karem, and B.T. Rouse, *DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology?* Crit Rev Immunol, 2017. **37**(2-6): p. 483-498.
36. Porter, K.R. and K. Raviprakash, *DNA Vaccine Delivery and Improved Immunogenicity.* Curr Issues Mol Biol, 2017. **22**: p. 129-138.
37. Li, L. and N. Petrovsky, *Molecular mechanisms for enhanced DNA vaccine immunogenicity.* Expert Rev Vaccines, 2016. **15**(3): p. 313-29.
38. Marc, M.A., E. Dominguez-Alvarez, and C. Gamazo, *Nucleic acid vaccination strategies against infectious diseases.* Expert Opin Drug Deliv, 2015. **12**(12): p. 1851-65.
39. Grunwald, T. and S. Ulbert, *Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases.* Clin Exp Vaccine Res, 2015. **4**(1): p. 1-10.
40. Tregoning, J.S. and E. Kinnear, *Using Plasmids as DNA Vaccines for Infectious Diseases.* Microbiol Spectr, 2014. **2**(6).
41. Williams, J.A., *Improving DNA vaccine performance through vector design.* Curr Gene Ther, 2014. **14**(3): p. 170-89.
42. Liu, M.A., *DNA vaccines: an historical perspective and view to the future.* Immunol Rev, 2011. **239**(1): p. 62-84.

43. Wahren, B. and M.A. Liu, *DNA Vaccines: Recent Developments and the Future.* Vaccines (Basel), 2014. **2**(4): p. 785-796wahren.
44. Ledgerwood, J.E. and B.S. Graham, *DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases.* Hum Vaccin, 2009. **5**(9): p. 623-6.
45. Keefer, M.C., et al., *Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network.* AIDS Res Hum Retroviruses, 1994. **10**(12): p. 1713-23.
46. Wu, F., et al., *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.* Medrxiv Preprint, 2020.
47. Martin, J.E., et al., *A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial.* Clin Vaccine Immunol, 2006. **13**(11): p. 1267-77.
48. Prud'homme, G.J., et al., *Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.* Curr Gene Ther, 2006. **6**(2): p. 243-73.
49. Hirao, L.A., et al., *Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques.* Vaccine, 2008. **26**(25): p. 3112-20.
50. Rosati, M., et al., *Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation.* Vaccine, 2008. **26**(40): p. 5223-9.
51. Curcio, C., et al., *DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice.* Cancer Gene Ther., 2008. **15**(2): p. 108-114.
52. Ugen, K.E., et al., *Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation.* Cancer Gene Ther., 2006. **13**(10): p. 969-974.
53. Tebas, P., et al., *Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report.* N Engl J Med, 2017.
54. Tebas, P., et al., *Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers.* J Infect Dis, 2019.
55. De Rosa, S.C., et al., *Robust antibody and cellular responses induced by DNA-only vaccination for HIV.* JCI Insight, 2020. **5**(13).
56. Chandrashekar, A., et al., *SARS-CoV-2 infection protects against rechallenge in rhesus macaques.* Science, 2020.
57. Patel, A., et al., *Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model.* bioRxiv, 2020: p. 2020.07.28.225649.
58. Andrade, V.M., et al., *INO-4800 DNA Vaccine Induces Neutralizing Antibodies and T cell Activity Against Global SARS-CoV-2 Variants.* bioRxiv, 2021: p. 2021.04.14.439719.
59. Gary E., W.B.M., Parzych E.M., Griffin B.D., Zhu X., Tailor N., Tursi N.J., Chan M., Purwar M., Vendramelli R., Choi J., Frost K.L, Reeder S., Liaw K., Tello E., Ali A.R., Yun K., Pei Y.,Thomas S.,Rghei A.D., Guilleman M.M., Muthumani K., Smith T., Wootton S.K., Patel A., Weiner D.B., Kobasa D., *A novel mouse AAV6 hACE2 transduction model of wild-type SARS-CoV-2 infection studied using synDNA immunogens.* iScience, 2021.
60. Gooch, K., et al., *One or two dose regimen of the SARS-CoV-2 synthetic DNA vaccine INO-4800 protects against respiratory tract disease burden in nonhuman primate challenge model.* Research Square 2021.
61. Trevor, S. *Development of INO-4800, a DNA-vaccine for COVID-19*. in *Keystone Symposia Antibodies and Vaccines as Drugs for COVID-19*. 2021.
62. Andrews, N., et al., *Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant.* New England Journal of Medicine, 2022.

63. Keeton, R., et al., *T cell responses to SARS-CoV-2 spike cross-recognize Omicron.* Nature, 2022.
64. European Commission, *Directorate-General: A Guideline on Summary of Product Characteristics (SmPC)*. 2009, EMA.
65. Diehl, M.C., et al., *Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers.* Hum Vaccin Immunother, 2013. **9**(10): p. 2246-52.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
	Bell's Palsy
	Transverse myelitis
	Narcolepsy
Hematologic	Thrombocytopenia
	Immune thrombocytopenia (ITP)
	Disseminated intravascular coagulation (DIC)
	Hemorrhagic stroke
	Non-hemorrhagic stroke
	Deep Vein Thrombosis (DVT)
	Pulmonary Embolism (PE)
Immunologic	Anaphylaxis
	Vasculitides
Cardiac	Acute cardiac failure
	Myocarditis/pericarditis
	Acute myocardial infarction
Other	Septic shock-like syndrome
	Appendicitis
	Multisystem Inflammatory Syndrome
	Acute kidney failure

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690
WHO UTN: U1111-1266-9952

Protocol Version: 1.0USA

Protocol Version Date: 30-Jul-2021

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted] Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 6.0, dated 30-Apr-2021, to Version 1.0USA, dated 30-Jul-2021. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

Based upon the increasing availability of EUA vaccine in the US and completion of the Phase 3 dose selection from the Phase 2 data, the Sponsor recognizes that subjects may want to receive a non-study prophylactic COVID-19 vaccine (either authorized under emergency use or when licensed). Therefore, the following change has been implemented:

- Receipt of a non-study prophylactic COVID-19 vaccine (authorized under emergency use or when licensed), for subjects in the Phase 2 segment of the trial, is removed from the restricted concomitant medications (see Section 6.4.7).

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 50 centers globally. Final country list to be determined.

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (placebo for INO-4800) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0
Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0 mg) or placebo (placebo for INO-4800). See Table 2 and Figure 1. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per U.S. Center for Disease Control (CDC) criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

Table 2: Phase 3 Segment

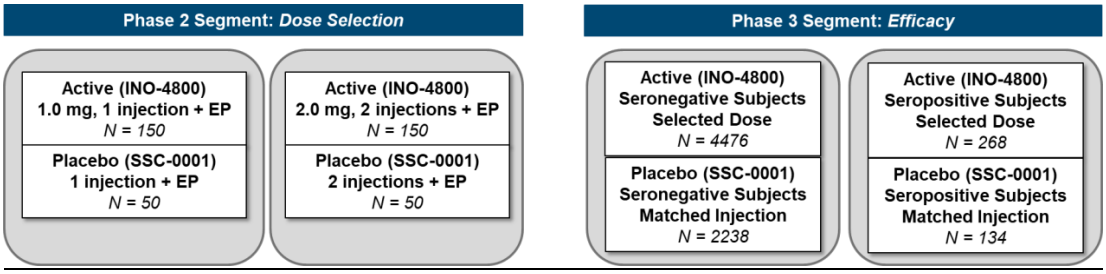
Treatment Arm	Sero status	Expected Number of Subjects	Approx. Expected Number of Subjects by Age Group		Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose of INO-4800 (mg)
			18-50	51+[a]					
INO-4800	Seroneg	4476	2238	2238	0, 28	2	1.0	2.0	4.0
	Seropos	268	134	134					
Placebo	Seroneg	2238	1119	1119	0, 28	2	0	0	0
	Seropos	134	67	67					
Total	**Seroneg**	6714	3357	3357					
	Seropos	402	201	201					
Total		7116							

[a]at least 711 subjects will be ≥65 years of age

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 3b. Antigen-specific cellular immune response such as measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding enzyme-linked immunosorbent assay (ELISA), pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot-forming assay (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (placebo for INO-4800) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms per the case definition or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Phase 2 segment: Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Phase 3 segment: Subjects at high risk for SARS-CoV-2 exposure including subjects at high risk for severe COVID-19 who are 18 years and older.

Inclusion Criteria: Phase 2 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly

5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;
        iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria: Phase 3 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary

staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria: Phase 2 segment

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;

d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Exclusion Criteria: Phase 3 segment

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (this criterion only applies after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, after which this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
    - Current or anticipated use of disease modifying doses of systemic 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) or others;
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: Two 1.0mg ID injections of INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Placebo: Two ID injections of placebo for INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (placebo for INO-4800)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swabs)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltoid muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swabs and saliva specimens at COVID-19 assessment and convalescent visits. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, in the subject’s vehicle or at the subject’s home and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)[k]	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[l]	COVID-19 convalescent visit[m]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[n]	X[n]
Height and Weight	X																
HIV Serology		X															
Pregnancy Test[c]	X	X			X												
INO-4800 or Placebo + EP[d]		X			X												
Download EP Data[e]			X			X											
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[g]		X					X				X				X	X[r]	X
Humoral Samples[h]		X					X				X				X	X[r]	X
SARS-CoV-2 Serology[i]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Nasopharyngeal swabs)		X														X[o]	
Distribute Diary[p]			X			X											
Review/Collect Diary[q]				X	X		X										

a. Screening assessment occurs from -30 days to -1 day of Day 0. Screening and Day 0 visits may be combined if eligibility is able to be confirmed prior to dosing. If so, all assessments for Screening and Day 0 must be performed at the combined visit.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.

c. In women of childbearing potential. Urine pregnancy test at all indicated visits.
d. Intradermal injection(s) in skin preferably over deltoid region, or alternately over anterolateral quadriceps region, followed by EP at Day 0 and Day 28.
e. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
f. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
g. On Day 0, cellular sampling requires 64 mL of whole blood prior to 1st dose. At all other time points, collect 32 mL of whole blood. Cellular samples will be collected at selected clinical sites (estimated to include 711 subjects)
h. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce four serum aliquots of 2 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each.
i. SARS-CoV-2 antibody.
j. The Day 0 RT-PCR results will not be required prior to dosing on that day.
k. Day 42 visit must occur at least 10 days after Day 28 visit.
l. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or at a home visit and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
m. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization
n. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.
o. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
p. Diaries to be used at selected sites only (estimated to include 711 subjects).
q. Diary should be reviewed at the 14-day post-dose phone call or visit and collected at the next in-office visit.
r. When possible, cellular and humoral immunology samples will be collected. Cellular samples will be collected at selected sites only.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Given the continued number of cases globally, SARS-CoV-2 infections remain a serious unmet medical concern. Appropriate measures to prevent SARS-CoV-2 infections, including its variants, are not yet widely available.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [2-4]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [5, 6]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [7, 8], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [9].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [10], associated with substantial morbidity and mortality [11]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [12]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid

test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [4] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities

include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [9].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [9].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19, however there are several vaccines that are available under Emergency Use Authorization (EUA) in the United States and other countries. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of new strains of SARS-CoV-2, an effective prophylactic vaccine ideally induces immunity against not only SARS-CoV-2 Wuhan-Hu-

1 but also its variants. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for additional vaccines for prevention of SARS-CoV-2 infections.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 3 (REVEAL1) randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer (NCT03185013) and several Phase 2 trials for related and other indications and several Phase 2 trials for related and other indications. We have additionally built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV vaccine candidate was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [33].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [34-43]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [42, 44]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [45]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research

in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [46].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [47]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

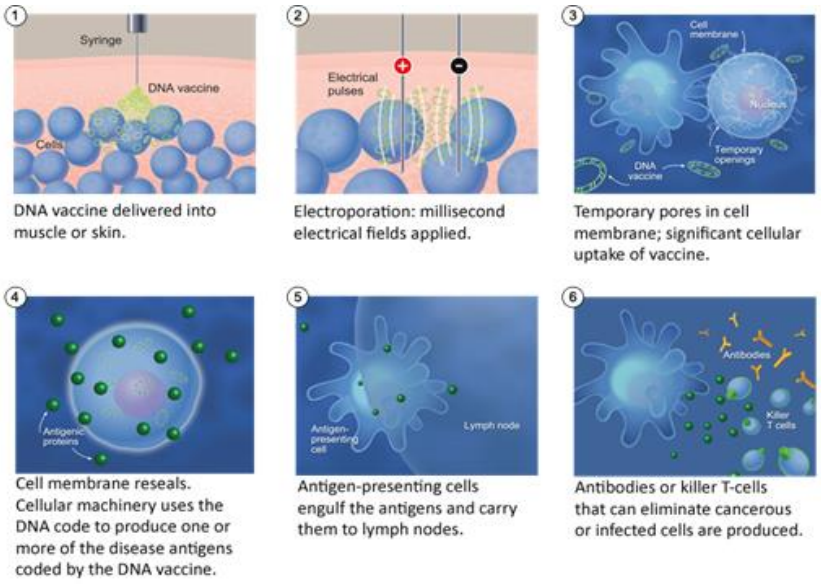
Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [48]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens for the activation of both cellular and humoral responses [49, 50]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [50]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [51, 52].

1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 Wuhan-Hu-1 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [53-55].

Following ID injection, the Inovio Pharmaceuticals' EP device [48] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES FOLLOWING VACCINATION WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [56]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [57].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11

adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of March 10, 2021, 35 related adverse events were reported cumulatively, of which all but three (Grade 2 injection site pruritus, lethargy and abdominal pain) were Grade 1 in severity.

Additional analyses showed that INO-4800 provides broad cross-reactive immune responses against variants of concern (VOC). Clinical samples, collected at varying timepoints post-immunization from subjects enrolled during Phase 1 INO-4800 clinical trial, were analyzed against the spike protein of different VOC (including UK variant B.1.1.7, South African variant B.1.351, and Brazilian variant P.1. strains) [58]. The results revealed neutralization activity against the P.1 variant (neutralizing antibodies levels comparable to those against wild-type) and reduced, but still measurable neutralization activity against the B.1.1.7 and B.1.351 variants. Additionally, it has been demonstrated that INO-4800 induces cross-reactive T cell responses against B.1.1.7, B.1.351, and P.1 variants that are comparable to the wild-type strain. Taken together, these data demonstrate that INO-4800 maintains cellular and/or humoral immune responses against the major SARS-CoV-2 variants that are currently in circulation, which will likely be critical factors necessary to impact the ongoing COVID-19 pandemic.

Please refer to the Investigator's Brochure, which will include future updates through the duration of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

This Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), to enable selection of a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >7000 subjects.

The current safety and immunogenicity data from the Phase 2 segment strongly support the selection and advancement of the 2.0 mg dose of INO-4800 into the Phase 3 segment (see Section 1.3.7 for immunogenicity details). INO-4800's competitive safety/tolerability profile, nonclinical data supporting its potential to confer durable protection against severe

disease, ability to serve as a safe and tolerable homologous booster, and thermostability profile collectively support its potential as an additional tool for COVID-19 prevention with distinct advantages to facilitate global distribution and uptake.

1.3.6.1 Safety and tolerability of INO-4800

Safety and tolerability data collected on INO-4800 to date mirror the favorable safety profile of Inovio's plasmid DNA vaccines against multiple targets and indications. Nonclinical studies have revealed no safety concerns. Clinical studies (Phase 1 and Phase 2) have also not revealed any safety concerns as per reviews by independent Data Safety Monitoring Boards.

1.3.6.2 Nonclinical INO-4800 Data in Support of Potential Efficacy

The efficacy of INO-4800 in protecting against SARS-CoV-2 disease has been demonstrated in multiple nonclinical models. In the AAV6 human ACE2-transduced mouse model challenged with SARS-CoV-2, complete protection against lung virus load was observed [59]. Applying clinically relevant dosing and CELLECTRA-ID delivery parameters, INO-4800 has been tested in multiple nonhuman primate models, the gold standard large animal model for COVID-19 vaccine testing. We demonstrated protection against lung disease and viral load in the lower and upper respiratory tract in the rhesus macaque model after one or two doses of INO-4800 [60][61]. Furthermore, the durability of the impact of INO-4800 in reducing lung viral load was demonstrated in a rhesus macaque challenged with SARS-CoV-2 several months after immunization [57]. In conclusion, multiple nonclinical models have demonstrated the efficacy of INO-4800.

1.3.6.3 Potential Role of INO-4800 as a Booster

INO-4800 offers a potential role in serving as a booster to maintain protection against COVID-19 over time in the context of a potential endemic disease scenario. Unlike viral vectors, DNA elicits no anti-vector response and, therefore, can be repeatedly administered without a reduction in the generated immune responses. When subjects in the INO-4800 Phase 1 were provided a booster dose 6 to 10.5 months following the 2-dose regimen, there was no appreciable change in reactogenicity when compared to the first two doses, indicating that repeat dosing with INO-4800, as with other vaccines in Inovio's DNA platform, does not lead to an increase in reactogenicity. Inovio's DNA platform experience with Oncology DNA-vaccine targets have established that more than 10 sequential administrations of vaccine is capable of consistent re-boosting from an immunological perspective with no associated changes in safety and reactogenicity.

1.3.6.4 Thermostability of INO-4800

INO-4800 offers thermostability that could facilitate vaccine distribution globally. The current shelf life applied to INO-4800 clinical supplies is 24 months when stored at its recommended refrigerated storage condition of 5 ± 3°C. A 24-month real-time study for INO-4800 under refrigerated conditions (5°C) is ongoing; current Month 9 results are all within specification. Percent supercoiled forms, which is the strongest indication of DNA plasmid stability, decreased by only 2% (T0 97%, M9 95%) over the duration of the study to date, while percent total circular forms remained at 99%.

Inovio has a platform stability program with 12 different DNA plasmid products, all constructed with the same plasmid backbone and formulated in the same SSC buffer, at various DNA concentrations, and the stability data to date are all consistent with the excellent stability profile seen with INO-4800.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. Based on Inovio's extensive experience developing vaccine candidates against infectious diseases via the ID route ([54], [33]), a 2-dose regimen was considered to be optimal, based on the balanced humoral and cellular responses obtained 2 weeks post-dose 2, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In the Phase 2 segment of this trial, 1.0 mg and 2.0 mg of vaccine were administered by ID injection and followed immediately by EP at Day 0 and Day 28. The selection of the doses to test in Phase 2 is supported by the safety profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) in addition to our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial was to further evaluate the 1.0 mg and 2.0 mg doses of INO-4800 for each age group in order to select the optimal vaccination regimen in the Phase 3 efficacy segment. The final decision between the two doses by age group relies on safety and immunogenicity. The 1.0 mg and 2.0 mg doses in the Phase 1 study had a similar safety profile. The review of the Phase 2 data by the independent DSMB has not revealed any safety signals of concern to date. Furthermore, there have not been substantial differences in the safety profile between the 1.0 mg and 2.0 mg dosing groups to impact Phase 3 dose selection. However, the interim immunology data from the Phase 2 study revealed favorable immunogenicity with the 2.0 mg dose over the 1.0 mg dose. Data were analyzed for two age groups: ≥18 to ≤50 years of age and ≥51 years of age. The results illustrate that the 2.0 mg dose induced higher levels of SARS-CoV-2 spike specific antibodies as well as higher levels of IFN-gamma producing cells.

1.3.7.1 Binding Antibody Response

The binding antibody response was measured for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the geometric mean titer (GMT) for the 1.0 mg dose group was 123.3 at Day 0 compared to 938.8 at Week 6. The geometric mean fold rise was 7.8. The GMT for the 2.0 mg dose group was 93.5 at baseline compared to 2210.0 at Week 6. The geometric mean fold rise was 23.5.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 148.5 at Day 0 compared to 1182.1 at Week 6. The geometric mean fold rise in binding antibody titers was 7.9. The GMT for the 2.0 mg dose group was 99.5 at baseline compared to 2671.2 at Week 6. The geometric mean fold rise was 26.5.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 87.5 at Day 0 compared to 623.3 at Week 6. The geometric mean fold rise in titers was 7.6. The GMT for the 2.0 mg dose group was 84.0 at baseline compared to 1613.7 at Week 6. The geometric mean fold rise in binding antibodies was 19.2.

1.3.7.2 Neutralizing Antibody Response

The neutralizing antibody response was measured for all Phase 2 subjects at Days 0 and Week 6. Across all ages the geometric mean titer (GMT) for the 1.0 mg dose group was 32.2 at Day 0 compared to 93.6 at Week 6. The geometric mean fold rise in neutralizing titers was 2.9. The GMT for the 2.0 mg dose group was 35.8 at baseline compared to 150.6 at Week 6. The geometric mean fold rise was 4.3.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 34.5 at Day 0 compared to 112.6 at Week 6. The geometric mean fold rise in neutralizing titers was 3.3. The GMT for the 2.0 mg dose group was 32.2 at baseline compared to 159.9 at week 6. The geometric mean fold rise was 5.0.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 28.4 at Day 0 compared to 67.4 at Week 6. The geometric mean fold rise in neutralizing titers was 2.3. The GMT for the 2.0 mg dose group was 43.3 at baseline compared to 135.7 at Week 6. The geometric mean fold rise was 3.2.

1.3.7.3 ELISPOT analysis

ELISPOT analysis was performed for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the median for the 1.0 mg dose group was 0 at Day 0 compared to 6.7 at Week 6. The median for the 2.0 mg dose group was 2.2 at baseline compared to 18.9 at Week 6. Subjects 18-50 years old in the 1.0 mg dose group had a median of that was 1.1 at Day 0 compared to 7.6 at Week 6. The median for the 2.0 mg dose group was 0.6 at baseline compared to 18.9 at Week 6. Subjects ≥51 years old in the 1.0 mg dose group had a median that was 0 at Day 0 compared to 10 at Week 6. The median for the 2.0 mg dose group was 3.3 at baseline compared to 18.4 at Week 6.

1.4 RISKS AND POTENTIAL BENEFITS

As of Dec 31, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile delineated in this section through the duration of the study.

1.4.1 POTENTIAL BENEFITS

As part of the trial, subjects will have access to COVID-19 diagnostic and antibody testing to which they might not otherwise have access. Additionally, subjects will have the benefit of contributing to research to help others in a time of a global pandemic. Benefits related to receipt of INO-4800 and protection from COVID-19 disease are unknown because the efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in TableTable~~Table~~5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness

Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v4.0, dated 16-Nov-2020
[b] EU commission guideline on the SmPC September 2009 [62]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of Dec. 31, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction
- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of Dec. 31, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)
- Cardiac arrhythmias (product-related); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g., electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;

- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that "Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment" is an exclusion criterion ('h') in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 OVERALL BENEFIT/RISK CONCLUSION

While EUA vaccines are currently becoming available in many countries, the global availability to the general population remains limited. In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio's DNA platform across all of its products, and INO-4800's Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies the conduct of the Phase 2/3 trial.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo (placebo for INO-4800). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0mg) or placebo (placebo for INO-4800). Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥ 51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence of or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per CDC criteria [1], as listed below:

- Cancer
- Chronic kidney disease

- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease, that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for Phase 3, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS

	2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINTS

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 3b. Antigen-specific cellular immune response measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (placebo for INO-4800) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the independent blinded EAC.

The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

*Local lab results will be accepted if the subject is hospitalized and a sample is not able to be obtained for analysis at central lab.

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:
  a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
  b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
  c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
  d. Significant acute renal, hepatic, or neurologic dysfunction,
  e. Admission to an ICU, or
  f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR SARS-COV-2 ASYMPTOMATIC INFECTION

Positive testing by SARS-CoV-2 serologic assay (performed at central lab);

- Without clinical signs or symptoms of COVID-19 disease since the previous negative serologic test.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*).* Assays such as binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

4.1.1 PHASE 2 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas

7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
10. Others, if approved by the medical monitor;

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 PHASE 3 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
   1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)

2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

4.2.1 PHASE 2 SEGMENT

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;

f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the prior 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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);
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;

n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.2.2 PHASE 3 SEGMENT

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:

   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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) or others;
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);

m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

If a subject decides to be vaccinated with a non-study prophylactic COVID-19 vaccine, either authorized under emergency use or licensed,during the trial, subjects should provide details of the non-study COVID-19 vaccine received to study staff and subjects should be requested to remain in the trial until the last visit. Additionally, subjects should also be advised that we do not have adequate information about the safety and effectiveness of another prophylactic COVID-19 vaccine when received following the receipt of INO-4800. As is already the case, if a subject is enrolled and receives a non-study prophylactic COVID-19 vaccine, either authorized under emergency use or licensed, while on study, the Investigator should enter the details as a concomitant medication. The subject should be followed (according to the Schedule of Events outlined in Table 3 of the Protocol).

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (placebo for INO-4800): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL or 0.8 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (placebo for INO-4800): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 0.8 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The

DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.
- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [63].
- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles. The Pulse Generator and ID Applicator are reusable components. These components should be cleaned and disinfected prior to each subject's use according to the Cleaning and Maintenance procedure in the User Manual. The Pulse Generator and ID Applicator have been validated for up to 30 cleaning and disinfection cycles based on a maximum of 30 subjects being treated in a day. Therefore, the Pulse Generator and ID Applicator's use should be limited to 30 subjects in a day. Any potential risk of damage to the device due to cleaning

and disinfection for more than 30 cycles has not been validated. Always inspect the device before use according to the instructions in the Maintenance section of the User Manual.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of placebo for INO-4800 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Two 1.0mg ID injections of INO-4800 (~0.1mL dose volume) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)
- Placebo: Two ID injections of placebo for INO-4800 (~0.1mL) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded throughout the trial. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

It is not deemed appropriate to unblind a subject's treatment assignment for the purpose of assisting the subject in making a decision regarding receipt a different COVID-19 vaccine (emergency use or licensed vaccine). Subjects should be advised that without efficacy data, INO-4800 has not been proven to be more protective than placebo in the prevention of COVID-19 and SARS-CoV-2 infection. Therefore, unblinding will not provide any meaningful information to inform a decision of receiving a different COVID-19 vaccine. The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for such an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. placebo for INO-4800 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 or 0.8 mL. placebo for INO-4800 is supplied in 2-mL vials at a minimum volume of 0.8 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or placebo for INO-4800. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or placebo for INO-4800 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4.) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration. Screening and Day 0 visits may be on the same day if eligibility is able to be confirmed prior to randomization. If so, all assessments for Screening and Day 0 must be performed at the combined visit.

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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics;
- Collect socio-behavioral assessment information (Section 6.4);

- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.6);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect urine for pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.8).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or having occurred within 3 months prior to Screening. Subjects should be queried about any history of Hepatitis B, Hepatitis C and HIV.

In the Phase 3 segment, subjects with a self-reported history of Hepatitis B or C must provide documentation of liver enzymes that are not significantly elevated within the past 3 months. If such a report of liver enzyme testing is not available, this testing should be performed at Screening. Subjects with a history of Hepatitis C without cirrhosis who have completed treatment and have proof of an undetectable viral load at least 12 weeks following treatment may be enrolled and do not require liver enzymes within the past months.

Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 or an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);
- Review restrictions for injection and EP (Section 6.4.7);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR (Day 0 only) (Section 6.4.8);
- Collect diary from Day 0 dose during Day 28 visit only(for selected sites only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data;
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide);
- Phase 2 segment: Distribute diary;
- Phase 3 segment, for selected sites: Distribute diary.

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);

Phase 2 segment only:

- Review diary (Section 6.4).

Phase 3 segment only:

- Review diary (for selected sites)(Section 6.4);

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5);

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect diary from Day 28 visit (for selected sites only);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.9);
- Record current concomitant medications/treatments (Section 6.4.6);

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 Day 201 visit only; Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 segment:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect urine pregnancy test (Section 6.4).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5).

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or at a home visit and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR testing from the central lab. A local RT-PCR result will be considered acceptable in the case where a subject is hospitalized and a sample for central lab analysis is not able to be obtained, if it was obtained using. an assay performed by a laboratory accredited according to standards set by a national or regional accreditation body.

If a local lab is used to confirm the case, the report from the laboratory must be provided.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 only:

- Collect whole blood and serum for cellular and humoral immunology assessment, where possible (Phase 3 cellular immunology collection at selected sites only) (Section 6.5)
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (Section 6.4.8).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 2 segment only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;

- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a site code and a subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4.).

At the COVID-19 assessment and convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

Blood samples will be collected at visits specified in the Schedule of Events (Tables 3 and 4). A total of approximately mL 245-330mL of blood will be drawn from each subject over the course of the study (inclusive of relevant safety and immunology samples at regular study visits per Tables 3 and 4). If the subject is evaluated at COVID-19 visits, an additional volume of approximately 85-120mL will be collected. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening (Phase 2 segment only).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Pregnancy Testing:

Pregnancy testing will be performed on women of childbearing potential (WOCBP). All women will be assumed to be of childbearing potential unless they are:

- Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
- Women who are surgically sterile or have a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of a vasectomy, subjects should wait six (6) months post-vasectomy to be considered sterile.

Phase 2: For WOCBP, a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit.

Phase 3: For WOCBP, a urine pregnancy test will be obtained at Screening and will be performed immediately prior to any dosing.

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 subject is pregnant prior to completing the specified dose regimen, then no further IP

will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol and at selected sites (estimated to include 711 subjects) in the Phase 3 segment. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the next study phone call or visit and collected at the next in-person study visit. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be assessed.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin

3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of each injection site with CELLECTRA® 2000 at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections must be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection on different limbs and subsequently followed immediately by EP of the injection site with CELLECTRA® 2000 at Day 0 and Day 28.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

In Phase 2, samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. All subjects will be observed for 30 minutes following the IP administration procedure for immediate AEs. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

	interference w/ activity			

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

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

[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription, including receipt of any non-study COVID-19 vaccine (authorized under emergency use or licensed)) taken between informed consent and study discharge (see Section 4.2) must be recorded on the CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.7) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.7 RESTRICTIONS

In the Phase 2 segment of the trial, subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1.1). In the Phase 3 segment of the trial, subjects should refrain from becoming pregnant until receipt of the last dose of investigation product by using appropriate contraceptive measures (See Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature ≥38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine during the trial. In the Phase 3 segment, subjects should not receive any other drug/vaccine intended as COVID-19 prophylaxis during the trial. Subjects should be reminded that if and when appropriate, the Sponsor would offer INO-4800 to those who received placebo in the trial if INO-4800 is demonstrated to be efficacious.

For subjects in the Phase 2 segment of the trial, the receipt of any non-study prophylactic COVID-19 vaccine (authorized under emergency use or licensed) is not restricted, based upon increasing availability of EUA vaccine in the US and completion of the Phase 3 dose selection from the Phase 2 data.

If a subject informs the site of their intent to receive a non-study prophylactic COVID-19 vaccine available either authorized under emergency use or when licensed, the subject should be informed that the safety and effectiveness of receiving INO-4800 followed by another COVID-19 vaccine has not been studied.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.8 SARS-CoV-2 Testing

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic or subject's vehicle or at the subject's home. During this visit, nasal swabs and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed. If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on nasopharyngeal specimens collected at Day 0. The Day 0 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

For subjects who are seronegative at baseline, if at any time during the trial, either the SARS-CoV-2 antibody or an RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or in the subject's home, nasopharyngeal swabs will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed on the sample(s) collected at the COVID-19 assessment visit.

6.4.9 COVID-19 Disease Monitoring

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches,

headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of ≥ 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or in the subject's home.

Subjects with a confirmed COVID-19 diagnosis, per the case definition outlined in Section 3.7, prior to dose 2 or who have a positive SARS-CoV-2 PCR test at Day 0 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell, or with sequelae that appear to be permanent.

Subjects who require medical care for COVID-19 (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

6.5 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4.) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires 32 mL of whole blood be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood for cellular sampling and 8 mL serum for humoral sampling is required on Day 0 prior to 1st dose. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

Humoral samples will be collected on all subjects and cellular samples will be collected at selected sites (from approximately 711 subjects). Both humoral and cellular analysis will be conducted in the first 102 subjects age 18-50 and in the first 102 subjects age 51 and older enrolled at the sites that are selected for cellular sample collection. In addition, cellular and humoral samples will be analyzed on all subjects with COVID-19 when samples are available.

The immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene

expression or flow cytometry, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;
- Confirmed COVID-19 disease.

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 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF;
- The Pregnancy outcomes of spontaneous abortion (miscarriage), ectopic pregnancy, fetal demise/stillbirth in a subject or subject partner following exposure to study treatment is considered to be 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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;
- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

The Investigator will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the Investigator'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 further administration of the investigational product in the clinical trial;
- Has accompanying or inducing symptoms or signs;
- Is judged by the Investigator 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The Investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment;
- Any Grade 4 AEs related to study treatment;
- Any report of anaphylaxis related to study treatment;
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

In the case of suspected Severe COVID-19 cases, the trial will be paused if a vaccine-to-placebo case split yields a relative risk with a 90% confidence interval lower bound >1. The minimum case split corresponding to this criterion is 8:0. In this scenario, the trial will pause until at least one additional case is accrued and the DSMB can review the data and make a recommendation regarding continued enrollment in the trial.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted], M.D.
Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the Investigator until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 Investigator 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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

Investigators should use correct medical terminology/concepts when recording AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 Investigator will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with CTCAE.

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 Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject’s response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator 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.

Investigators 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 Investigator 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 Investigator'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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the Investigator. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects in Phase 2 who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

Subjects in Phase 3 who are pregnant or expect to become pregnant prior to the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

The Investigator 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 dose administrations, must not be performed. The Investigator 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 Investigator if their partner becomes pregnant until study completion. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign a Pregnancy Information Collection Consent Form to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The site will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If an Investigator is contacted by the male subject or his pregnant partner, the Investigator 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including 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.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's primary endpoint is the incidence of virologically-confirmed COVID-19 disease in subjects who are SARS-CoV-2 seronegative at baseline starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, and cases among

baseline SARS-CoV-2 seropositive subjects. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern efficacy against variants, efficacy against asymptomatic infection, and binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% among baseline SARS-CoV-2 seronegative subjects will be tested with H_0: $p \geq .70/(.70+k)$ *vs*. H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population among those who are baseline SARS-CoV-2 seronegative will be primary for the analyses of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

Among subjects who are SARS-CoV-2 seronegative at baseline, the primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs*. H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.022 and the corresponding lower bound of the two-sided 95.6% CI for efficacy exceeds 30% (alpha-level adjusted for interim analyses, see Section 8.5.6), and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but with 95% CIs and without the hypothesis test p-value.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects and by baseline SARS-CoV-2 serostatus.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint.. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

8.5.3 **SAFETY ANALYSES**

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to the Phase of the trial. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.6 INTERIM ANALYSES

For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The two-sided type I error of 0.05 will not be adjusted for possible early stopping due to this aspect.

For the Phase 2 segment, group-level unblinded summaries of the immunogenicity and safety data will be produced once Week 6 visit immunology data and Week 8 visit safety data are complete for all subjects who have not discontinued, while maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all subjects who have not discontinued with remaining visits through the final visit. These summaries will allow the Sponsor to have results for the purposes of dose selection for the Phase 3 portion. No subject-level immunogenicity data will be produced, and subject-level immunogenicity data will not be available in the clinical trial database until all other clinical

trial data are finalized at the end of the trial. No safety summary will be provided if the total number of subjects who experience the event of interest is greater than 0 and the count of the number of subjects with the event in a given treatment group relative to the total produces a percentage less than 3%, for a given summary. The group-level unblinded production of the summaries will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

For the Phase 3 segment, there are two planned formal interim efficacy analyses: one at 50% (75 cases) and one at 75% (112 cases) of the total required for the primary endpoint (149 cases). The Lan-DeMets O'Brien-Fleming approximate alpha-spending function will be used for the efficacy and futility boundaries. As such, the first interim analysis will utilize a one-sided nominal alpha of 0.0016, and the second interim analysis will utilize a one-sided nominal alpha of 0.0092. The final analysis will utilize a one-sided nominal alpha of 0.022. The DSMB will be responsible for the interim evaluations. The unblinded interim analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

If the prespecified criteria for efficacy above are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until 4500 subjects have 6 months of safety follow-up. At that point, the trial would be unblinded, and subjects who received placebo will be offered the active product.

8.5.7 MULTIPLICITY

There is one primary hypothesis that will be tested. As there are two interim analyses of the primary endpoint, the type I error rate will be controlled at two-sided 0.05 by using the Lan-DeMets O'Brien-Fleming approximate alpha-spending function (see Section 8.5.6).

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Efficacy

Phase 3 segment

The exploratory efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but with a 95% CI and without the hypothesis test p-value.

8.5.9.2 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline increases in antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean fold-rises and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.3 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 149 observed cases among baseline SARS-CoV-2 seronegative subjects will be required to provide 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60% and utilizing the methodology described in Section 8.5.1 and Section 8.5.6 . A sample size of 6714 baseline SARS-CoV-2 seronegative subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

Phase 3 Segment

Subjects will be randomized (2 INO-4800:1 Placebo). Randomization will be stratified according to two factors, each with two levels: a) age-group age category (18-50 years vs. ≥51 years) on Day 0, and b) presence or absence on Day 0 of underlying medical conditions that increase risk of severe COVID-19 disease, per US CDC criteria.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

- Submit continuing review reports to the IRB/REB/EC as required, and request re-review and approval of the clinical trial at least once a year during the conduct of the clinical trial;
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects;
- Notify the IRB/REB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events;
- Obtain approval from the IRB/REB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required;
- Submit reports on, and reviews of, the clinical trial and its progress to the IRB/REB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines;
- Maintain a file of clinical trial-related information (refer to clinical trial files) that includes all correspondence with the IRB/REB/EC;

- Notify the IRB/REB/EC when the clinical trial is completed (i.e., after the last clinical trial visit of the final clinical trial subject);
- After clinical trial completion (within three [3] months is recommended), provide the IRB/REB/EC with a final report on the clinical trial.

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately.

Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion.

If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
  - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
  - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor of this study. The Department of Defense, Joint Program Executive Office is providing funding for the Phase 2 segment of the study and Inovio is providing funding for the Phase 3 segment. Clinical trial insurance has been taken out according to 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 per ICH E6 R1.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot-forming assay
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

16.0 REFERENCES

1. Centers for Disease Control and Prevention. *People with Certain Medical Conditions*. March 29, 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
2. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. **92**(4): p. 401-402.
3. Hui, D.S., et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.* Int J Infect Dis, 2020. **91**: p. 264-266.
4. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
5. GenBank. *Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome*. 2020; Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.
6. Smith, T.R.F., et al., *Immunogenicity of a DNA vaccine candidate for COVID-19.* Nat Commun, 2020. **11**(1): p. 2601.
7. World Health Organization, *Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance.* 2020.
8. World Health Organization, *Novel Coronavirus (2019-nCoV) Situation Report*. 2020.
9. Wiersinga, W.J., et al., *Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.* JAMA, 2020.
10. World Health Organization, *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. March 11, 2020.
11. Zou, L., et al., *SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.* N Engl J Med, 2020.
12. Center for Systems Science and Engineering at Johns Hopkins University, *COVID-19 Dashboard*. 2020.
13. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Intern Med, 2020.
14. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* Chin J Epidemiol, 2020. **41**(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
17. Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* Lancet, 2020. **395**(10223): p. 514-523.
18. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.* N Engl J Med, 2020. **382**(10): p. 970-971.
19. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020.* Euro Surveill, 2020. **25**(17).
20. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020. **26**(5): p. 672-675.

21. Liu, Y., et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus.* J Travel Med, 2020. **27**(2).
22. Centers for Disease Control and Prevention. *Symptoms of Coronavirus*. 2020 March 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
23. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* N Engl J Med, 2020.
24. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ, 2020. **369**: p. m1375.
25. Centers for Disease Control and Prevention. *COVID-19 Pandemic Planning Scenarios*. July 10, 2020 July 20, 2020 July 27, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
26. Lipsitch, M., et al., *Transmission dynamics and control of severe acute respiratory syndrome.* Science, 2003. **300**(5627): p. 1966-70.
27. Peiris, J.S., et al., *Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.* Lancet, 2003. **361**(9371): p. 1767-72.
28. Tsang, T.K., et al., *Influenza A Virus Shedding and Infectivity in Households.* J Infect Dis, 2015. **212**(9): p. 1420-8.
29. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
30. Long, Q.X., et al., *Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.* Nat Med, 2020.
31. Diao, B., et al., *Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19).* Front Immunol, 2020. **11**: p. 827.
32. Grifoni, A., et al., *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.* Cell, 2020. **181**(7): p. 1489-1501 e15.
33. Modjarrad, K., et al., *Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial.* Lancet Infect Dis, 2019. **19**(9): p. 1013-1022.
34. Suschak, J.J., J.A. Williams, and C.S. Schmaljohn, *Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity.* Hum Vaccin Immunother, 2017. **13**(12): p. 2837-2848.
35. Manickan, E., K.L. Karem, and B.T. Rouse, *DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology?* Crit Rev Immunol, 2017. **37**(2-6): p. 483-498.
36. Porter, K.R. and K. Raviprakash, *DNA Vaccine Delivery and Improved Immunogenicity.* Curr Issues Mol Biol, 2017. **22**: p. 129-138.
37. Li, L. and N. Petrovsky, *Molecular mechanisms for enhanced DNA vaccine immunogenicity.* Expert Rev Vaccines, 2016. **15**(3): p. 313-29.
38. Marc, M.A., E. Dominguez-Alvarez, and C. Gamazo, *Nucleic acid vaccination strategies against infectious diseases.* Expert Opin Drug Deliv, 2015. **12**(12): p. 1851-65.
39. Grunwald, T. and S. Ulbert, *Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases.* Clin Exp Vaccine Res, 2015. **4**(1): p. 1-10.
40. Tregoning, J.S. and E. Kinnear, *Using Plasmids as DNA Vaccines for Infectious Diseases.* Microbiol Spectr, 2014. **2**(6).
41. Williams, J.A., *Improving DNA vaccine performance through vector design.* Curr Gene Ther, 2014. **14**(3): p. 170-89.
42. Liu, M.A., *DNA vaccines: an historical perspective and view to the future.* Immunol Rev, 2011. **239**(1): p. 62-84.

43. Wahren, B. and M.A. Liu, *DNA Vaccines: Recent Developments and the Future.* Vaccines (Basel), 2014. **2**(4): p. 785-796wahren.
44. Ledgerwood, J.E. and B.S. Graham, *DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases.* Hum Vaccin, 2009. **5**(9): p. 623-6.
45. Keefer, M.C., et al., *Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network.* AIDS Res Hum Retroviruses, 1994. **10**(12): p. 1713-23.
46. Wu, F., et al., *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.* Medrxiv Preprint, 2020.
47. Martin, J.E., et al., *A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial.* Clin Vaccine Immunol, 2006. **13**(11): p. 1267-77.
48. Prud'homme, G.J., et al., *Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.* Curr Gene Ther, 2006. **6**(2): p. 243-73.
49. Hirao, L.A., et al., *Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques.* Vaccine, 2008. **26**(25): p. 3112-20.
50. Rosati, M., et al., *Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation.* Vaccine, 2008. **26**(40): p. 5223-9.
51. Curcio, C., et al., *DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice.* Cancer Gene Ther., 2008. **15**(2): p. 108-114.
52. Ugen, K.E., et al., *Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation.* Cancer Gene Ther., 2006. **13**(10): p. 969-974.
53. Tebas, P., et al., *Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report.* N Engl J Med, 2017.
54. Tebas, P., et al., *Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers.* J Infect Dis, 2019.
55. De Rosa, S.C., et al., *Robust antibody and cellular responses induced by DNA-only vaccination for HIV.* JCI Insight, 2020. **5**(13).
56. Chandrashekar, A., et al., *SARS-CoV-2 infection protects against rechallenge in rhesus macaques.* Science, 2020.
57. Patel, A., et al., *Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model.* bioRxiv, 2020: p. 2020.07.28.225649.
58. Andrade, V.M., et al., *INO-4800 DNA Vaccine Induces Neutralizing Antibodies and T cell Activity Against Global SARS-CoV-2 Variants.* bioRxiv, 2021: p. 2021.04.14.439719.
59. Gary E., W.B.M., Parzych E.M., Griffin B.D., Zhu X., Tailor N., Tursi N.J., Chan M., Purwar M., Vendramelli R., Choi J., Frost K.L, Reeder S., Liaw K., Tello E., Ali A.R., Yun K., Pei Y.,Thomas S.,Rghei A.D., Guilleman M.M., Muthumani K., Smith T., Wootton S.K., Patel A., Weiner D.B., Kobasa D., *A novel mouse AAV6 hACE2 transduction model of wild-type SARS-CoV-2 infection studied using synDNA immunogens.* iScience, 2021.
60. Gooch, K., et al., *One or two dose regimen of the SARS-CoV-2 synthetic DNA vaccine INO-4800 protects against respiratory tract disease burden in nonhuman primate challenge model.* Research Square 2021.
61. Trevor, S. *Development of INO-4800, a DNA-vaccine for COVID-19*. in *Keystone Symposia Antibodies and Vaccines as Drugs for COVID-19*. 2021.
62. European Commission, *Directorate-General: A Guideline on Summary of Product Characteristics (SmPC)*. 2009, EMA.

63. Diehl, M.C., et al., *Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers.* Hum Vaccin Immunother, 2013. **9**(10): p. 2246-52.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
	Bell's Palsy
	Transverse myelitis
	Narcolepsy
Hematologic	Thrombocytopenia
	Immune thrombocytopenia (ITP)
	Disseminated intravascular coagulation (DIC)
	Hemorrhagic stroke
	Non-hemorrhagic stroke
	Deep Vein Thrombosis (DVT)
	Pulmonary Embolism (PE)
Immunologic	Anaphylaxis
	Vasculitides
Cardiac	Acute cardiac failure
	Myocarditis/pericarditis
	Acute myocardial infarction
Other	Septic shock-like syndrome
	Appendicitis
	Multisystem Inflammatory Syndrome
	Acute kidney failure

COVID19-311

Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

INNOVATE
(Inovio INO-4800 Vaccine Trial for Efficacy)

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 19690
WHO UTN: U1111-1266-9952

Protocol Version: 2.0USA

Protocol Version Date: 08-Oct-2021

Medical Monitor Approval Page

Drug: INO-4800

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

Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

[Electronically signed]

[redacted]Jr., M.D., FACP, FIDSA [redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

CONFIDENTIAL

The information in this document is considered privileged and confidential by Inovio Pharmaceuticals Inc. (INOVIO) and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval and informed consent, or as required by local regulatory authorities. Persons to whom this information is disclosed must be informed that this information is privileged and confidential and that it should not be further disclosed without the written permission of INOVIO. Any supplemental information added to this document is also confidential and proprietary information of INOVIO and must be kept in confidence in the same manner as the contents of this document.

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 is a list of significant changes from Version 1.0USA, dated 30-Jul-2021, to Version 2.0USA, dated 08-Oct-2021. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific integrity of the protocol.

- Based upon the wide availability of EUA and licensed vaccines in the US and completion of the data collection towards the Phase 3 dose selection, the Sponsor recognizes that subjects may want to know whether they received INO-4800 or placebo in order to make fully informed choices about receiving a non-study prophylactic COVID-19 vaccine (either authorized under emergency use or when licensed). Therefore, the Phase 2 segment of the study will be unblinded after all subjects have reached the Week 30 Visit timepoint.
- Clarifications have been included within the stopping rules (Section 7.8.4) to clarify that stopping rules apply to both IP and device related events.
- Clarifications have been included within the instructions for reporting of device-related complaints or deficiencies (Section 7.13) to clarify that the Sponsor will review any reported device complaints for potential hazards that could cause an SAE and determine whether the Safety Review Committee (SRC) Chair should be notified.

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Phase 2/3 Randomized, Blinded, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of INO-4800, a Prophylactic Vaccine against COVID-19 Disease, Administered Intradermally Followed by Electroporation in Adults at High Risk of SARS-CoV-2 Exposure

Protocol Number: COVID19-311

Clinical Trial Phase: 2/3

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately 50 centers globally. Final country list to be determined.

Background:
INO-4800 is a prophylactic vaccine under development against SARS-CoV-2, the causative agent of COVID-19. INO-4800 contains the plasmid pGX9501, which encodes for the full length of the Spike glycoprotein of SARS-CoV-2. The goal of this trial is to assess the safety, immunogenicity and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

Clinical Trial Design:
This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by intradermal (ID) injection followed immediately by electroporation (EP) using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose of INO-4800 in the Phase 2 segment for a subsequent efficacy evaluation in the Phase 3 segment.

Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either active investigational product (INO-4800) or placebo (placebo for INO-4800) according to Table 1 below. Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Table 1: Phase 2 Segment Dose Groups

Study Group	Expected Number of Subjects	Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose (mg)
INO-4800	150	0, 28	1	1.0	1.0	2.0
INO-4800	150	0, 28	2[a]	1.0	2.0	4.0
Placebo	50	0, 28	1	0	0	0
Placebo	50	0, 28	2[a]	0	0	0
Total	**400**					

[a]INO-4800 or placebo will be injected ID followed immediately by EP in an acceptable location on two different limbs at each dosing visit.

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0 mg) or placebo (placebo for INO-4800). See Table 2 and Figure 1. Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per U.S. Center for Disease Control (CDC) criteria [1], as listed below:

- Cancer
- Chronic kidney disease
- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

Table 2: Phase 3 Segment

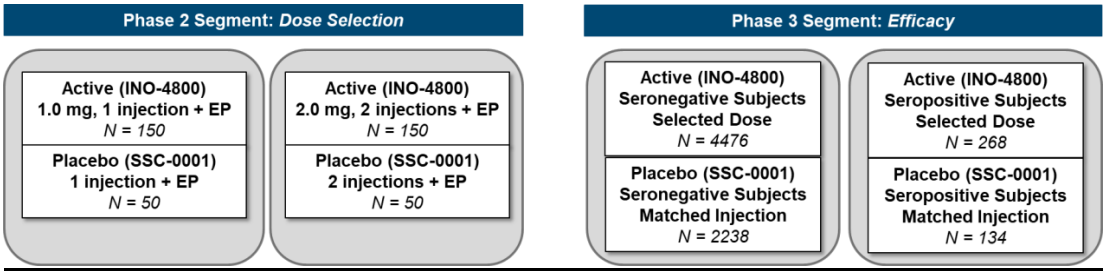
Treatment Arm	Sero status	Expected Number of Subjects	Approx. Expected Number of Subjects by Age Group		Dosing Days	Number of Injections + EP per Dosing Visit	INO-4800 (mg) per injection	INO-4800 (mg) per Dosing Visit	Total Dose of INO-4800 (mg)
			18-50	51+[a]					
INO-4800	Seroneg	4476	2238	2238	0, 28	2	1.0	2.0	4.0
	Seropos	268	134	134					
Placebo	Seroneg	2238	1119	1119	0, 28	2	0	0	0
	Seropos	134	67	67					
Total	**Seroneg**	6714	3357	3357					
	Seropos	402	201	201					
Total		7116							

[a]at least 711 subjects will be ≥65 years of age

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

Figure 1: Enrollment and Dose Group Design



External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for the Phase 3 segment, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

Criteria for Evaluation:

Research Hypothesis:

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

Phase 2 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Secondary Objective	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability

Phase 3 Segment Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
Secondary Objectives	**Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class

	(SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline
Exploratory Objective	**Exploratory Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels 3b. Antigen-specific cellular immune response such as measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

Immunogenicity Assessment:

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*)*. Assays such as binding enzyme-linked immunosorbent assay (ELISA), pseudovirus-based neutralization assay, and enzyme-linked immunosorbent spot-forming assay (ELISpot) will be evaluated at serial timepoints.

Safety Assessment:

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. Adverse events (AEs), regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, Medically Attended Adverse Events (MAAEs) and AESIs will be collected from time of consent until EOS. SAEs, AESIs and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

Efficacy Assessment (Phase 3 segment only):

Subjects will receive either active investigational product (INO-4800) or placebo (placebo for INO-4800) in a 2-dose regimen administered on Days 0 and 28 intradermally followed immediately by EP. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms per the case definition or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the EAC.

Clinical Trial Population:

Phase 2 segment: Healthy subjects at high risk for SARS-CoV-2 exposure who are 18 years and older.

Phase 3 segment: Subjects at high risk for SARS-CoV-2 exposure including subjects at high risk for severe COVID-19 who are 18 years and older.

Inclusion Criteria: Phase 2 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly

5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure
10. Others, if approved by the medical monitor.

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
    1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
    2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
    3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
        i. hormonal contraception including implants, injections or oral;
        ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
        iii. intrauterine device or intrauterine system;
        iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria: Phase 3 segment

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary

staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)
2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria: Phase 2 segment

a. Acute febrile illness with temperature >100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;

d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;
f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Medical conditions as follows:
    - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
    - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
    - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
    - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
    - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
    - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed);
    - Current or anticipated use of disease modifying doses of systemic 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);
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the past 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Exclusion Criteria: Phase 3 segment

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (this criterion only applies after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, after which this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:
    - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
    - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
    - Current or anticipated use of disease modifying doses of systemic 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) or others;
    - History of solid organ or bone marrow transplantation;
    - History of or current receipt of any other clinically significant immunosuppressive drugs
    - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);

- Any metal implants or implantable medical device within the electroporation site;

j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

Clinical Trial Treatment:

Phase 2 Segment

Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Placebo: One or two ID injection(s) of saline sodium citrate buffer (SSC-0001) (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

Active Investigational Product: Two 1.0mg ID injections of INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Placebo: Two ID injections of placebo for INO-4800 followed immediately by EP administered in separate limbs at Day 0 and Day 28 (±3 days)

Formulation:

INO-4800 is formulated in sodium chloride and sodium citrate buffer, refrigerated. Placebo [sterile saline sodium citrate buffer (placebo for INO-4800)], refrigerated.

TABLE 3 – PHASE 2 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk 6	Tel #3	Wk 30	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 7 (±3d)	Day 28 (±3d)		Phone call - Day 35 (±3d)	Day 42 (±5d)	Phone Call - Day 56 (±5d)	Day 210 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[m]	COVID-19 convalescent visit[n]
		Pre	Post		Pre	Post							
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical history	X	X											
Demographics	X												
Socio-behavioral Assessment	X												
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X
Physical Exam[b]	X	X			X			X		X	X	X	X
Vital Signs	X	X			X			X		X	X	X[p]	X[p]
Height and Weight	X												
CBC with differential[c]	X	X			X			X			X		
Chemistry[c]	X	X			X			X			X		
HIV Serology		X											
Urinalysis Routine[d]	X	X			X			X			X		
Pregnancy Test[e]	X	X			X						X		
INO-4800 or Placebo + EP[f]		X			X								
Download EP Data[g]			X			X							
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[i]		X						X		X	X		X
Humoral Samples[j]		X						X		X	X		X
SARS-CoV-2 Serology[k]	X												
SARS-CoV-2 RT-PCR (Saliva and Swabs)	X[l]											X[l]	X[l]
Distribute Diary			X			X							
Review/Collect Diary[o]				X	X		X	X					

a. Screening assessment occurs from -30 days to -1 day of Day 0.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.
c. Hemoglobin A1c collected at screening only. Chemistry includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, alkaline phosphatase, AST, ALT, LDH, total bilirubin.
d. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
e. Serum pregnancy test at Screening. Urine pregnancy test at other visits.
f. Intradermal injection(s) in skin preferably over deltoid muscle, or alternately over anterolateral quadriceps muscle, followed by EP at Day 0 and Day 28.
g. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
h. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
i. On Day 0, cellular sampling requires 64 mL of whole blood (8 Cell Preparation Tubes (CPT), each 8 mL of whole blood) prior to 1st dose. At all other time points, collect 32 mL of whole blood (4 CPT tubes, each 8 mL of whole blood).
j. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce eight serum aliquots of 1 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce four serum aliquots of 1 mL each.
k. SARS-CoV-2 antibody.
l. Saliva specimen at Screening; Nasal swabs and saliva specimens at COVID-19 assessment and convalescent visits. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
m. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, in the subject’s vehicle or at the subject’s home and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
n. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing, the site should follow up with the subject via phone call or an unscheduled visit after symptom resolution or stabilization.
o. Diary should be reviewed at the 7-day post-dose phone call and collected at the next in-office visit.
p. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.

TABLE 4 – PHASE 3 SEGMENT SCHEDULE OF EVENTS

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk 6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk 42	Tel #14-16	Wk 56	Illness	Illness
	Screen[a]	Day 0		Phone call - Day 14 (±3d)	Day 28 (±3d)		Day 42 (±5d)[k]	Phone call - Days 56, 70, 84, 98, 112 (±5d)	Day 126 (±5d)	Phone calls - Days 140, 154 168, 182, 196 (±5d)	Day 210 (±5d)	Phone calls - Days 238, 266 (±5d)	Day 294 (±5d)	Phone calls Days 322, 350, 378 (±5d)	Day 393 (± 5d)	COVID-19 assessment visit[l]	COVID-19 convalescent visit[m]
		Pre	Post		Pre	Post											
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Medical history	X	X															
Demographics	X																
Socio-behavioral Assessment	X																
Concomitant Medications	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[b]	X	X			X		X		X		X		X		X	X	X
Vital Signs	X	X			X		X		X		X		X		X	X[n]	X[n]
Height and Weight	X																
HIV Serology		X															
Pregnancy Test[c]	X	X			X												
INO-4800 or Placebo + EP[d]		X			X												
Download EP Data[e]			X			X											
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellular Samples[g]		X					X				X				X	X[r]	X
Humoral Samples[h]		X					X				X				X	X[r]	X
SARS-CoV-2 Serology[i]	X	X			X		X		X		X		X		X		X
SARS-CoV-2 RT-PCR (Nasopharyngeal swabs)		X														X[o]	
Distribute Diary[p]			X			X											
Review/Collect Diary[q]				X	X		X										

a. Screening assessment occurs from -30 days to -1 day of Day 0. Screening and Day 0 visits may be combined if eligibility is able to be confirmed prior to dosing. If so, all assessments for Screening and Day 0 must be performed at the combined visit.
b. Full physical examination only at Screening and Day 393 (or EOS). Targeted physical exam at other indicated visits.

c. In women of childbearing potential. Urine pregnancy test at all indicated visits.
d. Intradermal injection(s) in skin preferably over deltoid region, or alternately over anterolateral quadriceps region, followed by EP at Day 0 and Day 28.
e. Following administration of INO-4800 or placebo, EP data will be downloaded from the CELLECTRA® 2000 device and provided to Inovio.
f. AEs to be collected from time of consent to Day 56; SAEs, MAAEs, and AESIs to be collected from time of consent to EOS.
g. On Day 0, cellular sampling requires 64 mL of whole blood prior to 1st dose. At all other time points, collect 32 mL of whole blood. Cellular samples will be collected at selected clinical sites (estimated to include 711 subjects)
h. On Day 0, humoral sampling requires a total of 17 mL of whole blood (two 10-mL red top serum collection tubes, each 8.5 mL of whole blood, to produce four serum aliquots of 2 mL each). At all other time points, collect 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each.
i. SARS-CoV-2 antibody.
j. The Day 0 RT-PCR results will not be required prior to dosing on that day.
k. Day 42 visit must occur at least 10 days after Day 28 visit.
l. Subjects will be evaluated during a “COVID-19 assessment visit” when acute COVID-19 is suspected. The assessment visit may be performed in the clinic, subject’s vehicle, or at a home visit and should be completed within 3 days of symptom onset or within 3 days of a positive result of a SARS-CoV-2 test.
m. For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, the date of positive SARS-CoV-2 test. If acute symptoms are ongoing the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization
n. Vital signs to be performed at COVID-19 assessment and convalescent visits include temperature, respiration rate, heart rate and oxygen saturation.
o. Genotyping may also be performed on sample(s) collected at the COVID-19 assessment visit.
p. Diaries to be used at selected sites only (estimated to include 711 subjects).
q. Diary should be reviewed at the 14-day post-dose phone call or visit and collected at the next in-office visit.
r. When possible, cellular and humoral immunology samples will be collected. Cellular samples will be collected at selected sites only.

1.0 INTRODUCTION

This document is a protocol for a human research trial to be conducted according to U.S. and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Given the continued number of cases globally, SARS-CoV-2 infections remain a serious unmet medical concern. Appropriate measures to prevent SARS-CoV-2 infections, including its variants, are not yet widely available.

1.2 BACKGROUND INFORMATION

In late 2019, a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei province, China [2-4]. These cases were announced on January 6, 2020 as testing negative for influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). On January 7, 2020 a novel virus was isolated by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and the isolate was named "Wuhan-Hu-1." The gene sequence of that isolate was then generated and determined to be of a novel coronavirus [5, 6]. That gene sequence was publicly posted on January 10, and the novel coronavirus was preliminarily named 2019-nCoV. Subsequently, on February 11, 2020, the virus was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) [7, 8], due to its similarity with the original SARS virus. That same day, the World Health Organization (WHO) announced a specific name of the disease, "COVID-19," associated with infection by this novel coronavirus, as based on the novel coronavirus origin and year of first reported cases. The first cluster of human cases identified comprised people who worked, visited, or lived around the local Huanan seafood wholesale market in Wuhan, where live animals and fresh meat and fish were on sale, suggesting that an animal was the source of the novel respiratory virus being transmitted to humans.

Epidemiologic data suggest that droplets expelled during face-to-face exposure during talking, coughing, or sneezing is the most common mode of transmission while contact surface spread remains yet another possible mode of transmission [9].

SARS-CoV-2 infection rapidly emerged as a global threat to public health, joining other coronavirus-related diseases, such as SARS and MERS. COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) by the WHO on January 20, 2020, and was declared a pandemic on March 11, 2020 [10], associated with substantial morbidity and mortality [11]. As of July 25, 2020, a total of nearly 16 million laboratory-confirmed COVID-19 cases have been reported internationally, including over 643,000 deaths [12]. However, given the lack of widespread testing, the true number of cases of COVID-19 is likely far higher than reported. Preliminary results from large U.S.-based seroepidemiological surveys indicate an estimated incidence rate of SARS-CoV-2 infections to be 6 to 24 times that of the number of reported cases of COVID-19 [13].

An article in *JAMA* by Wu and McGoogan [14] provided a summary of a major report by the Chinese Center for Disease Control and Prevention (China CDC) [15]. Of a total of 72,314 case records, 44,672 (62%) were confirmed as SARS-CoV-2 infections based on positive viral nucleic acid test results on throat swabs, 16,186 (22%) as suspected cases based on symptoms and exposures only, 10,567 (15%) as clinically diagnosed based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, and 889 (1%) as asymptomatic cases based on a positive viral nucleic acid

test result but lacking typical symptoms including fever, dry cough, and fatigue [16]. The overall case-fatality ratio (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions - 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [16]. These initial reports of the CFR documented the level of seriousness of COVID-19.

Given the novelty of SARS-CoV-2, its rapid spread among humans and its associated morbidity and mortality, there has been an explosion of epidemiological, clinical, virologic, and other scientific data regarding the propagation of effects of this virus emerging from China, the United States, and many other countries. These data have established that 1) SARS-CoV-2 is transmitted person-to-person [17], even from those who are asymptomatic or presymptomatic [18-20], 2) the virus is very infectious, with estimates of the R_0 (Reproductive number) ranging from 1.50 to 6.49, with a mean average of 3.28 and a median average of 2.79 [21], 3) the constellation of symptoms, signs, and an incubation period ranging between 2 and 14 days [22], and 4) the asymptomatic proportion of those infected being substantial, perhaps as high as 80% [17, 23-25]. Further, research has found that the risk of death from COVID-19 increases with age and with serious, comorbid conditions including hypertension, diabetes, cardiovascular disease, obesity, etc.

Finally, although much has been learned very quickly about SARS-CoV-2 and COVID-19, much more is still to be determined. The aforementioned CFR and similar estimates are from crude analyses that have only accounted for moderate to serious cases. Therefore, the true CFR is likely significantly lower. Further, the infection-fatality ratio (IFR), which is the proportion who die among all those infected regardless of any symptomology, is likely still even lower than the CFR, but both the CFR and IFR will not be known with certainty until well-designed and controlled seroepidemiology surveys have been conducted using well-validated antibody assays and thorough questionnaires to obtain symptom history. Also, the presence of natural immunity of those infected who survive and the durability of such natural immunity is to be determined. Thus, the existence and possibility of reinfection and recurrent infection is unknown.

1.2.1 CLINICAL PRESENTATION, TRANSMISSION AND IMMUNE RESPONSE

A study in *The Lancet* by Huang and colleagues [4] reported the epidemiological, clinical, laboratory, and radiological characteristics, as well as treatment and clinical outcomes, of patients with laboratory-confirmed COVID-19 pneumonia. Common symptoms at onset of illness were fever (n=40, 98% of 41 patients), cough (n=31, 76%), and myalgia or fatigue (n=18, 44%); less common symptoms were sputum production (n=11, 28% of 39 patients), headache (n=3, 8% of 38 patients), hemoptysis (n=2, 5% of 39 patients), and diarrhea (n=1, 3% of 38 patients). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea was 8 days [Interquartile range 5 - 13 days]). Twenty-six (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT scan. Complications included acute respiratory distress syndrome (n=12, 29%), RNAaemia (n=6, 15%), acute cardiac injury (n=5, 12%) and secondary infection (n=4, 10%).

Wiersinga et al. summarized the common symptoms of COVID-19 in hospitalized patients as fever (70-90%), dry cough (60-86%), shortness of breath (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia and ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19. Common laboratory abnormalities

include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-alpha, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen). Common radiographic findings include bilateral, lower lobe infiltrates on chest radiographic imaging and bilateral, peripheral, lower-lobe ground-glass opacities and/or consolidation on chest computed tomographic imaging [9].

Transmission of SARS-CoV-2 occurred mainly after days of illness [26] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [27]. Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Analysis of these samples suggested that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza [28] and appears different from that seen in patients infected with SARS-CoV [27]. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients [11]. The SARS-CoV-2 transmission time window from COVID-19 patients is perhaps 2 days before symptom onset up to 37 days after symptom onset [20]. It is estimated that 48% to 62% of transmission may occur via presymptomatic carriers [9].

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10-15 days following the onset of COVID-19 symptoms. Seow et al. observed seroconversion in >95% with neutralizing antibody responses when sampled beyond 8 days after onset of symptoms [29]. However, declining neutralizing antibody titers were observed during the follow-up period. Long, et al, when following 37 asymptomatic individuals and 37 symptomatic patients into the early convalescent phase, observed that the IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined during the early convalescent phase [30]. T cells play a critical role in antiviral immunity but their numbers and functional state in SARS-CoV-2 infected patients remain largely unclear. Diao and colleagues performed a retrospective review of total T cell counts, and $CD4^+$ and $CD8^+$ T cell subsets based on inpatient data from 522 patients with laboratory-confirmed SARS-CoV-2 infection and 40 healthy controls in Wuhan from December 2019 to January 2020. T cell numbers including total T cells, CD4+ and CD8+ T cells in the severe and critical disease groups as well as those who died were significantly lower than in the mild/moderate disease group. Most importantly, the numbers of total T cells, CD8+ T cells and CD4+ T cells in severe COVID-19 cases, including those who died, were lower suggesting that there is a profound T cell loss in COVID-19 disease. Counts of total T cells, $CD8^+$ T cells or $CD4^+$ T cells were negatively correlated with patient survival [31].

It is quite likely that CD4+ T cell, CD8+ T cell, and neutralizing antibody all contribute to clearance of the acute infection. There is an ongoing need to understand the magnitude and composition of the human CD4+ and CD8+ T cell responses to SARS-CoV-2. If natural infection with SARS-CoV-2 elicits potent CD4+ and CD8+ T cell responses commonly associated with protective antiviral immunity, COVID-19 is a strong candidate for rapid vaccine development [32].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Currently, there is no licensed prophylactic vaccine against COVID-19, however there are several vaccines that are available under Emergency Use Authorization (EUA) in the United States and other countries. Numerous vaccine efforts are underway. Given the growing concerns regarding the emergence of new strains of SARS-CoV-2, an effective prophylactic vaccine ideally induces immunity against not only SARS-CoV-2 Wuhan-Hu-

1 but also its variants. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for additional vaccines for prevention of SARS-CoV-2 infections.

1.3 RATIONALE FOR PROPHYLACTIC VACCINE DEVELOPMENT

SARS-CoV-2 has become a pandemic resulting in substantial morbidity and mortality. Due to rapid spread of SARS-CoV-2 infections even from asymptomatic and mildly infected patients, there is an urgent need for appropriate measures to prevent, control and treat SARS-CoV-2 infections.

To address this critical need for a medical countermeasure for prevention of COVID-19 disease, we at Inovio Pharmaceuticals have employed our synthetic DNA-based vaccine technology. This technology is highly amenable to accelerated developmental timelines, due to the ability to rapidly design multiple test constructs, manufacture large quantities of the drug product, and leverage established regulatory pathways to the clinic. Furthermore, this technology platform has demonstrated proof of concept efficacy and safety in humans in a Phase 3 (REVEAL1) randomized, double-blind, placebo-controlled study for human papillomavirus (HPV) associated cervical pre-cancer (NCT03185013) and several Phase 2 trials for related and other indications and several Phase 2 trials for related and other indications. We have additionally built upon our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine to accelerate the development of a SARS-CoV-2 vaccine candidate. In a Phase 1 clinical study, the MERS-CoV vaccine candidate was safe and well tolerated, eliciting immune responses in more than 85% of participants after two vaccinations that were durable through 1 year of follow-up [33].

1.3.1 DNA VACCINES

Since the 1990s, a novel approach to vaccination against a broad array of target antigens and diseases has been in development. This involves the direct introduction of plasmid deoxyribonucleic acid (DNA) containing the gene encoding the immunogen against which an immune response is sought into appropriate host tissues and the *in situ* production of the target immunogen(s). This approach offers a combination of potential advantages, including the stimulation of both B- and T-cell responses, stability of the vaccine across a broad temperature range, absence of infectivity of the immunogen itself, the speed with which the vaccine can be constructed (for example in the face of an epidemic or pandemic as it is the case here with SARS-CoV-2), and the relative ease and generic nature of large-scale manufacture. Many scientific publications have addressed the potential of DNA vaccination [34-43]. Immune responses in animal models have been obtained using genes from a variety of infectious agents including influenza viruses, hepatitis B virus, human immunodeficiency virus, human papillomaviruses, Marburg virus, MERS coronavirus, rabies virus, SARS coronavirus, West Nile virus (WNV), Zika virus, and other infectious agents as plasmodium, mycoplasma, and many more [42, 44]. In many cases, protection from disease in animal models has also been demonstrated.

DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses against certain pathogens, as well as enabling cross-strain specific responses when many antibody responses are strain-specific. Because the encoded protein is synthesized *in vivo* by the host following administration, DNA vaccines can encode membrane-bound proteins instead of solely the soluble versions [45]. This can be important because key neutralizing epitopes are located in regions that would be excluded, or not formed in a monomeric truncated soluble version. Some early research

in COVID-19 control has already suggested that neutralizing antibodies may not be sufficient and that cell-mediated immunity may be necessary [46].

Unlike certain other vectors (such as heterologous viral vectors), DNA vaccines do not stimulate adaptive immune responses against themselves, although the DNA itself does stimulate certain innate immune responses [47]. In other words, they do not generate anti-vector immunity that could stunt antigen-specific responses following multiple exposures.

1.3.2 USE OF ELECTROPORATION WITH DNA VACCINES

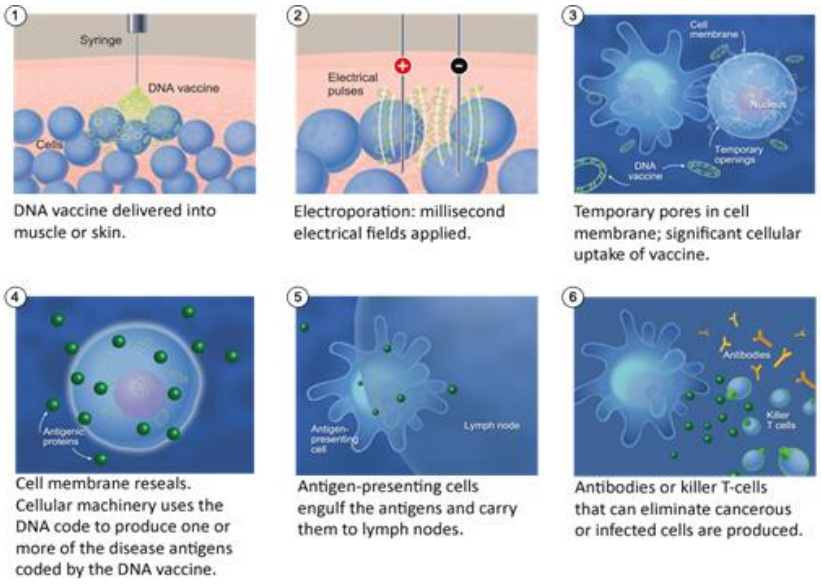
Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration (Figure 2). Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient production of the proteins encoded by the DNA expression plasmid system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [48]. EP has been extensively tested in animal species such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens for the activation of both cellular and humoral responses [49, 50]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [50]. IM and ID delivery of DNA vaccines with EP has been studied extensively, and optimum conditions for plasmid uptake and expression have been described for therapeutic indications, vaccines and tumor animal model systems [51, 52].

1.3.3 INOVIO'S PROPRIETARY TECHNOLOGY AGAINST COVID-19

Inovio Pharmaceuticals has developed INO-4800 as a DNA vaccine that contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 Wuhan-Hu-1 full length Spike glycoprotein. The ID route of delivery has been selected for INO-4800 based on recent findings from multiple DNA vaccine development programs where ID delivery has driven equivalent if not superior humoral and cellular responses to IM delivery while improving tolerability (clinicaltrials.gov NCT02464670, clinicaltrials.gov NCT02431767) [53-55].

Following ID injection, the Inovio Pharmaceuticals' EP device [48] referred to as the CELLECTRA® 2000 for ID administration (3P-ID) device is used to facilitate DNA entry into the cells.

Figure 2: The Potential Mechanism of Action Underlying Electroporation



1.3.4 NONHUMAN PRIMATE (NHP) CHALLENGE STUDIES FOLLOWING VACCINATION WITH INO-4800

NHPs are a valuable model in the development of COVID-19 vaccines and therapeutics as they can be infected with wild-type SARS-CoV-2, and present with early infection that mimics aspects of human disease [56]. Rhesus macaques (n=5) received two immunizations of INO-4800 (1.0 mg), at Week 0 and Week 4. Naïve control animals (n=5) did not receive vaccine. Humoral and cellular immune responses were monitored for 15 weeks (~4 months) following prime immunization for memory responses. All animals seroconverted following a single INO-4800 immunization, with serum IgG titers detected against the full-length S1+S2 extracellular domain (ECD), S1, S2, and receptor binding domain (RBD) regions of the SARS-CoV-2 S protein.

INO-4800 immunized macaques and unvaccinated controls were challenged with SARS-CoV-2 13 weeks (~3 months) post-final immunization. NHPs received a challenge dose of 1.1x104 PFU of SARS-CoV-2 by intranasal and intratracheal inoculation. Peak viral RNA loads in the BAL were significantly lower in the INO-4800 vaccinated group, along with significantly lower viral RNA loads at day 7 post-challenge, indicating protection from lower respiratory disease. While RNA was detected in the nasal swabs of both the control and INO-4800 vaccinated animals, viral mRNA levels trended downwards in INO-4800 vaccinated animals by more than 2 logs and were achieved sooner on average. Overall, the reduced viral loads following exposure to SARS-CoV-2 infection at 17 weeks after immunization show an important durable impact mediated by the vaccine [57].

1.3.5 FIRST-IN-HUMAN PHASE 1 TRIAL OF INO-4800

In the open-label, Phase 1 clinical trial, we initially evaluated the safety and immunogenicity of INO-4800 in 40 healthy participants, 18-50 years of age. There were two groups of 20 participants each who received either 1.0 mg or 2.0 mg of INO-4800 intradermally followed by EP at 0 and 4 weeks. In the first 40 subjects, by Week 8, 11

adverse events were reported of which all were Grade 1 in severity of which 6 were related to study drug. The frequency of AEs did not increase with the second administration.

From the immunogenicity analysis of the initial 40 subjects enrolled, two subjects were excluded from the analysis, one due to early discontinuation prior to the Week 4 dose for non-study reasons and the other due to suspected exposure to SARS-CoV-2 before the first dose of INO-4800 was administered based on a baseline positive SARS-CoV-2 serology. Thirty-eight (38) evaluable subjects had cellular and/or humoral immune responses following the second dose of INO-4800. Assessment of data from both Week 6 and Week 8 ELISpot revealed that 74% and 100% of the subjects generated T cell responses in the 1.0 mg and 2.0 mg groups, respectively. By Week 6, 95% (36 of 38) of the participants seroconverted by generating binding and/or neutralizing antibodies. Overall, INO-4800 elicited antigen-specific humoral and cellular immune responses against the SARS-CoV-2 Spike protein while demonstrating favorable safety and tolerability.

The protocol was amended to include an additional 80 healthy participants to evaluate safety and immunogenicity of INO-4800 in older and elderly age populations. A lower dose level (0.5 mg) was also added for evaluation of dose-sparing potential. A total of 40 participants were enrolled into three dose levels (0.5 mg, 1.0 mg and 2.0 mg), such that each Group included 20 participants 18-50 years of age, 10 participants 51-64 years of age, and 10 participants 65 years of age and older. Doses were delivered intradermally followed by EP at 0 and 4 weeks. As of March 10, 2021, 35 related adverse events were reported cumulatively, of which all but three (Grade 2 injection site pruritus, lethargy and abdominal pain) were Grade 1 in severity.

Additional analyses showed that INO-4800 provides broad cross-reactive immune responses against variants of concern (VOC). Clinical samples, collected at varying timepoints post-immunization from subjects enrolled during Phase 1 INO-4800 clinical trial, were analyzed against the spike protein of different VOC (including UK variant B.1.1.7, South African variant B.1.351, and Brazilian variant P.1. strains) [58]. The results revealed neutralization activity against the P.1 variant (neutralizing antibodies levels comparable to those against wild-type) and reduced, but still measurable neutralization activity against the B.1.1.7 and B.1.351 variants. Additionally, it has been demonstrated that INO-4800 induces cross-reactive T cell responses against B.1.1.7, B.1.351, and P.1 variants that are comparable to the wild-type strain. Taken together, these data demonstrate that INO-4800 maintains cellular and/or humoral immune responses against the major SARS-CoV-2 variants that are currently in circulation, which will likely be critical factors necessary to impact the ongoing COVID-19 pandemic.

Please refer to the Investigator's Brochure, which will include future updates through the duration of the study.

1.3.6 PROPOSED PHASE 2/3 TRIAL OF INO-4800

This Phase 2/3 trial is designed to begin with a Phase 2 segment to evaluate both the 1.0 mg and 2.0 mg doses in approximately 400 subjects, including in the older (51 to 64 years of age) and elderly subjects (65 years of age and older), to enable selection of a dose or age-related doses for an efficacy evaluation in a subsequent Phase 3 segment involving >7000 subjects.

The current safety and immunogenicity data from the Phase 2 segment strongly support the selection and advancement of the 2.0 mg dose of INO-4800 into the Phase 3 segment (see Section 1.3.7 for immunogenicity details). INO-4800's competitive safety/tolerability profile, nonclinical data supporting its potential to confer durable protection against severe

disease, ability to serve as a safe and tolerable homologous booster, and thermostability profile collectively support its potential as an additional tool for COVID-19 prevention with distinct advantages to facilitate global distribution and uptake.

1.3.6.1 Safety and tolerability of INO-4800

Safety and tolerability data collected on INO-4800 to date mirror the favorable safety profile of Inovio's plasmid DNA vaccines against multiple targets and indications. Nonclinical studies have revealed no safety concerns. Clinical studies (Phase 1 and Phase 2) have also not revealed any safety concerns as per reviews by independent Data Safety Monitoring Boards.

1.3.6.2 Nonclinical INO-4800 Data in Support of Potential Efficacy

The efficacy of INO-4800 in protecting against SARS-CoV-2 disease has been demonstrated in multiple nonclinical models. In the AAV6 human ACE2-transduced mouse model challenged with SARS-CoV-2, complete protection against lung virus load was observed [59]. Applying clinically relevant dosing and CELLECTRA-ID delivery parameters, INO-4800 has been tested in multiple nonhuman primate models, the gold standard large animal model for COVID-19 vaccine testing. We demonstrated protection against lung disease and viral load in the lower and upper respiratory tract in the rhesus macaque model after one or two doses of INO-4800 [60][61]. Furthermore, the durability of the impact of INO-4800 in reducing lung viral load was demonstrated in a rhesus macaque challenged with SARS-CoV-2 several months after immunization [57]. In conclusion, multiple nonclinical models have demonstrated the efficacy of INO-4800.

1.3.6.3 Potential Role of INO-4800 as a Booster

INO-4800 offers a potential role in serving as a booster to maintain protection against COVID-19 over time in the context of a potential endemic disease scenario. Unlike viral vectors, DNA elicits no anti-vector response and, therefore, can be repeatedly administered without a reduction in the generated immune responses. When subjects in the INO-4800 Phase 1 were provided a booster dose 6 to 10.5 months following the 2-dose regimen, there was no appreciable change in reactogenicity when compared to the first two doses, indicating that repeat dosing with INO-4800, as with other vaccines in Inovio's DNA platform, does not lead to an increase in reactogenicity. Inovio's DNA platform experience with Oncology DNA-vaccine targets have established that more than 10 sequential administrations of vaccine is capable of consistent re-boosting from an immunological perspective with no associated changes in safety and reactogenicity.

1.3.6.4 Thermostability of INO-4800

INO-4800 offers thermostability that could facilitate vaccine distribution globally. The current shelf life applied to INO-4800 clinical supplies is 24 months when stored at its recommended refrigerated storage condition of 5 ± 3°C. A 24-month real-time study for INO-4800 under refrigerated conditions (5°C) is ongoing; current Month 9 results are all within specification. Percent supercoiled forms, which is the strongest indication of DNA plasmid stability, decreased by only 2% (T0 97%, M9 95%) over the duration of the study to date, while percent total circular forms remained at 99%.

Inovio has a platform stability program with 12 different DNA plasmid products, all constructed with the same plasmid backbone and formulated in the same SSC buffer, at various DNA concentrations, and the stability data to date are all consistent with the excellent stability profile seen with INO-4800.

1.3.7 DOSE AND REGIMEN RATIONALE

The intent is to evaluate INO-4800 as a prophylactic vaccine against COVID-19 disease. Based on Inovio's extensive experience developing vaccine candidates against infectious diseases via the ID route ([54], [33]), a 2-dose regimen was considered to be optimal, based on the balanced humoral and cellular responses obtained 2 weeks post-dose 2, which supports evaluation of a 2-dose regimen (Days 0 and 28).

In the Phase 2 segment of this trial, 1.0 mg and 2.0 mg of vaccine were administered by ID injection and followed immediately by EP at Day 0 and Day 28. The selection of the doses to test in Phase 2 is supported by the safety profile in the Phase 1 trial of INO-4800 (COVID19-001, NCT04336410) in addition to our prior experience in developing a MERS coronavirus (MERS-CoV) vaccine (INO-4700) [16, 17]. The safety data for INO-4800 is provided in the Investigator's Brochure (IB).

The objective of the Phase 2 segment of the Phase 2/3 trial was to further evaluate the 1.0 mg and 2.0 mg doses of INO-4800 for each age group in order to select the optimal vaccination regimen in the Phase 3 efficacy segment. The final decision between the two doses by age group relies on safety and immunogenicity. The 1.0 mg and 2.0 mg doses in the Phase 1 study had a similar safety profile. The review of the Phase 2 data by the independent DSMB has not revealed any safety signals of concern to date. Furthermore, there have not been substantial differences in the safety profile between the 1.0 mg and 2.0 mg dosing groups to impact Phase 3 dose selection. However, the interim immunology data from the Phase 2 study revealed favorable immunogenicity with the 2.0 mg dose over the 1.0 mg dose. Data were analyzed for two age groups: ≥18 to ≤50 years of age and ≥51 years of age. The results illustrate that the 2.0 mg dose induced higher levels of SARS-CoV-2 spike specific antibodies as well as higher levels of IFN-gamma producing cells.

1.3.7.1 Binding Antibody Response

The binding antibody response was measured for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the geometric mean titer (GMT) for the 1.0 mg dose group was 123.3 at Day 0 compared to 938.8 at Week 6. The geometric mean fold rise was 7.8. The GMT for the 2.0 mg dose group was 93.5 at baseline compared to 2210.0 at Week 6. The geometric mean fold rise was 23.5.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 148.5 at Day 0 compared to 1182.1 at Week 6. The geometric mean fold rise in binding antibody titers was 7.9. The GMT for the 2.0 mg dose group was 99.5 at baseline compared to 2671.2 at Week 6. The geometric mean fold rise was 26.5.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 87.5 at Day 0 compared to 623.3 at Week 6. The geometric mean fold rise in titers was 7.6. The GMT for the 2.0 mg dose group was 84.0 at baseline compared to 1613.7 at Week 6. The geometric mean fold rise in binding antibodies was 19.2.

1.3.7.2 Neutralizing Antibody Response

The neutralizing antibody response was measured for all Phase 2 subjects at Days 0 and Week 6. Across all ages the geometric mean titer (GMT) for the 1.0 mg dose group was 32.2 at Day 0 compared to 93.6 at Week 6. The geometric mean fold rise in neutralizing titers was 2.9. The GMT for the 2.0 mg dose group was 35.8 at baseline compared to 150.6 at Week 6. The geometric mean fold rise was 4.3.

Subjects 18-50 years old in the 1.0 mg dose group had a GMT that was 34.5 at Day 0 compared to 112.6 at Week 6. The geometric mean fold rise in neutralizing titers was 3.3. The GMT for the 2.0 mg dose group was 32.2 at baseline compared to 159.9 at week 6. The geometric mean fold rise was 5.0.

Subjects ≥51 years old in the 1.0 mg dose group had a GMT that was 28.4 at Day 0 compared to 67.4 at Week 6. The geometric mean fold rise in neutralizing titers was 2.3. The GMT for the 2.0 mg dose group was 43.3 at baseline compared to 135.7 at Week 6. The geometric mean fold rise was 3.2.

1.3.7.3 ELISPOT analysis

ELISPOT analysis was performed for all Phase 2 subjects at Day 0 and Week 6. Across all ages, the median for the 1.0 mg dose group was 0 at Day 0 compared to 6.7 at Week 6. The median for the 2.0 mg dose group was 2.2 at baseline compared to 18.9 at Week 6. Subjects 18-50 years old in the 1.0 mg dose group had a median of that was 1.1 at Day 0 compared to 7.6 at Week 6. The median for the 2.0 mg dose group was 0.6 at baseline compared to 18.9 at Week 6. Subjects ≥51 years old in the 1.0 mg dose group had a median that was 0 at Day 0 compared to 10 at Week 6. The median for the 2.0 mg dose group was 3.3 at baseline compared to 18.4 at Week 6.

1.4 RISKS AND POTENTIAL BENEFITS

As of Dec 31, 2020, no treatment related serious adverse events have been reported for INO-4800. There may be side effects and discomforts that are not yet known.

Please refer to the Investigator's Brochure and User Manual, which will include future updates of the risk profile delineated in this section through the duration of the study.

1.4.1 POTENTIAL BENEFITS

As part of the trial, subjects will have access to COVID-19 diagnostic and antibody testing to which they might not otherwise have access. Additionally, subjects will have the benefit of contributing to research to help others in a time of a global pandemic. Benefits related to receipt of INO-4800 and protection from COVID-19 disease are unknown because the efficacy of INO-4800 remains unknown.

1.4.2 PRODUCT RISKS

1.4.2.1. Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

In accordance with the International Council for Harmonisation (ICH), Inovio-sponsored studies have been designed to minimize risk to study participants. Expected risks of INO-4800 delivered ID followed by EP with the CELLECTRA® 2000 device are listed below in Table5.

Table 5: Expected Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device[a]

Frequency among subjects[b]	Event
Very Common (≥10%)	• Injection site pruritus • Injection site erythema or redness • Injection site pain[c] or tenderness

Common (≥1% to <10%)	• Injection site bruising • Injection site swelling or induration
Uncommon or Rare (<1%)	• Administration site lesions or bleeding • Temporary severe injection site pain or tenderness

[a] Investigator's Brochure v4.0, dated 16-Nov-2020
[b] EU commission guideline on the SmPC September 2009 [62]
[c] Brief muscle contractions may occur and could be uncomfortable

1.4.2.2 Theoretical Risks of INO-4800 Delivered ID followed by EP using the CELLECTRA® 2000 Device

The following adverse events have been observed at least once, as of Dec. 31, 2020, across all clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device:

- Allergic reaction
- Anxiety
- Creatine phosphokinase (CPK) elevations that are transient
- Injection site infection, paresthesia, hypoesthesia, hematoma, or scab
- Vasovagal reaction, lightheadedness or dizziness.

The following events have not been observed, as of Dec. 31, 2020, in any subject or any clinical trials with Inovio DNA products delivered intradermally followed by EP using the CELLECTRA® 2000 device. While considered theoretical and unlikely to occur, any occurrence of these events should be reported to the Sponsor during this trial:

- Antibody-dependent enhancement of disease (i.e., potential for greater respiratory disease upon exposure to SARS-CoV-2 due to priming of immune cells from prior vaccination. Although observed in nonclinical models for vaccines against other viruses such as SARS, the occurrence or observation of antibody-dependent enhancement of the disease with COVID-19 vaccines in humans remains unknown)
- Cardiac arrhythmias (product-related); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Death (product-related);
- Disruption of function of implanted electronic medical device(s); Please note that "ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)" is an exclusion criterion ('j') in this protocol;
- Effects on fetus and/or pregnancy; Please note inclusion criterion in this protocol which requires use of medically effective contraception in women of childbearing potential;
- Electrical injury (e.g., electrocution); Please note warning within the device User Manual (Section 7). Since the device is not connected to any power supply during the EP procedure of a subject, this theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). This will be mitigated through device training and user qualification prior to use;

- Fire hazard to the facility; This theoretical event is unlikely but has the potential to occur to the clinical trial site. The possibility of this event has been mitigated through device design;
- Hearing damage (product-related); The possibility of this event has been mitigated through the device design. The audio is limited in volume and is of very short duration.
- Inaccurate energy delivery, the result of which is covered in other events listed here (e.g., tissue damage);
- Injection site laceration; This has not been observed but would be theoretically possible with any needle;
- Major injury to deeper tissue and/or bone; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Muscle damage; This event is not foreseeable given the array needle length is limited to 3.2 mm;
- Paresis or paralysis with possible loss of nerve function; There are minor nerves innervating the skin and subcutaneous tissues that may be disrupted, but are extremely unlikely to result in serious injury;
- Radiation hazard to eyes and skin; This theoretical event is unlikely but has the potential to occur to the user of the device (e.g., study site staff). The possibility of this event has been mitigated through the device design;
- Tissue injury/burn;
- User/subject unaware that treatment was incomplete;
- Worsening of unstable cardiac disease; Please note that "Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment" is an exclusion criterion ('h') in this protocol.

There have been no AEs associated with EP errors or failures.

1.4.3 OVERALL BENEFIT/RISK CONCLUSION

While EUA vaccines are currently becoming available in many countries, the global availability to the general population remains limited. In the context of the ongoing COVID-19 pandemic resulting in substantial morbidity and mortality, the overall cumulative safety profile of Inovio's DNA platform across all of its products, and INO-4800's Phase 1 adverse events being generally limited to local injection site reactions, the benefit risk profile justifies the conduct of the Phase 2/3 trial.

2.0 OBJECTIVES AND PURPOSE

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity and efficacy of INO-4800.

2.1 HYPOTHESIS

INO-4800 delivered ID followed immediately by EP will be well-tolerated, exhibit an acceptable safety profile, result in generation of cellular and humoral immune responses to SARS-CoV-2 Spike glycoprotein and provide protection against virologically-confirmed COVID-19 disease in subjects at high risk of SARS-CoV-2 exposure.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the safety, immunogenicity, and efficacy of INO-4800, administered by ID injection followed immediately by EP using the CELLECTRA® 2000 device, in a 2-dose regimen (Days 0 and 28) in adults who are at high risk of SARS-CoV-2 exposure. Subjects 18 years of age and older are expected to be enrolled across two (2) segments of this study. In the Phase 2 segment, approximately 400 seronegative subjects will be enrolled. In the Phase 3 segment, approximately 6714 seronegative subjects are expected to be enrolled, and 402 seropositive subjects will be enrolled. The subjects and data from Phase 2 are independent from that of Phase 3. The primary objectives of this trial are to identify in seronegative subjects an optimal age-related dose (Phase 2 segment) for subsequent evaluation for efficacy (Phase 3 segment).

Phase 2 Segment – Dose Selection

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be evaluated across four (4) dose groups (Table 1, Figure 1). Subjects will be randomized at a 3:3:1:1 ratio to receive either 1.0 mg or 2.0 mg of active investigational product (INO-4800) or 1 or 2 injections of placebo (placebo for INO-4800). Dose groups receiving INO-4800 will enroll approximately 150 subjects per group. Dose groups receiving placebo will enroll approximately 50 subjects per group. Randomization will be such that approximately 240 subjects aged 18-50 years, 120 subjects aged 51-64 years and 40 subjects aged ≥ 65 years will be enrolled. Initial enrollment will include subjects aged 18-50 years. Initiation of enrollment of older subjects 51-64 years of age and elderly subjects 65 years and older will depend on review of safety and immunogenicity data from those age groups generated in the Phase 1 study (COVID19-001).

Dose selection for evaluation of efficacy in the Phase 3 segment will be based on Week 6 immunogenicity data and Week 8 safety data from the Phase 2 segment. Group-level unblinded summaries and analyses of safety will be produced once the Week 8 phone call visit data are completed for all subjects in the Phase 2 segment. Group-level unblinded summaries and analyses of immunogenicity will be produced once the Week 6 visit data are completed for all subjects in the Phase 2 segment. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment – Efficacy

In the Phase 3 segment, approximately 6714 seronegative and 402 seropositive subjects 18 years of age and older will be randomized at a 2:1 ratio to receive either active investigational product (INO-4800, 2.0mg) or placebo (placebo for INO-4800). Approximately half of seronegative subjects and approximately half of seropositive subjects will be 18-50 years of age, and the other half will be ≥ 51 years of age as is operationally feasible. Also, approximately 711 subjects will be ≥65 years of age, if operationally feasible.

Subjects will be randomized in a stratified manner according to (a) age category (18-50 years vs. ≥51 years) on Day 0, and (b) presence of or absence on Day 0 of any of the following underlying medical conditions that increase risk of severe COVID-19 disease, per CDC criteria [1], as listed below:

- Cancer
- Chronic kidney disease

- Chronic lung diseases, including Chronic obstructive pulmonary disease (COPD), asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, pulmonary hypertension
- Neurologic conditions including stroke or cerebrovascular disease, that do not impact cognition
- Diabetes (type 1 or type 2)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- HIV infection (CD4 count >200 cells/mm3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

This segment of the trial is case-driven. Among seronegative subjects, a total of 149 observed cases will be required for 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60%. A sample size of 6714 seronegative subjects is expected to be required to achieve the 149 cases assuming an underlying attack rate of 3.7%. The actual sample size may differ if the observed attack rate is different than projected. There are two formal interim analyses of efficacy; one when 50% of the cases accrue and one when 75% of the cases accrue. If the prespecified criteria for efficacy are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until at least those 4500 subjects have a minimum of 6 months of safety follow-up. At that point, the trial would be unblinded and placebo-recipients will be offered the active product.

The primary efficacy endpoint window will begin 14 days post-dose 2 and will end at 12 months post-dose 2. All Phase 3 segment subjects will be followed for 56 weeks from the Day 0 dosing [i.e., Week 56 will be the planned End of Study (EOS) visit for this segment of the trial].

External Committee Reviews

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion. Additionally, for Phase 3, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

Details of each committee's scope will be provided in the respective charters.

3.1 PRIMARY OBJECTIVES

See Table 6.

3.2 PRIMARY ENDPOINTS

Table 6: Primary Objectives and Associated Endpoints

Phase 2 Primary Objective	Phase 2 Primary Endpoints
1. Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP	1a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot assay 1b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
Phase 3 Primary Objective	**Phase 3 Associated Primary Endpoint**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline	1. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline

3.3 SECONDARY OBJECTIVES

See Table 7.

3.4 SECONDARY ENDPOINTS

Table 7: Secondary Objectives and Associated Endpoints

Phase 2 Secondary Objectives	Phase 2 Secondary Endpoints
1. Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs)
Phase 3 Secondary Objectives	**Phase 3 Secondary Endpoints**
1. Evaluate the safety and tolerability of INO-4800	1a. Incidence of solicited and unsolicited injection site reactions 1b. Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product 1c. Incidence of serious adverse events (SAEs) 1d. Incidence of adverse events of special interest (AESIs) 1e. Incidence of all-cause mortality
2. Evaluate efficacy of INO-4800 in the prevention of COVID-19 disease according to degrees of disease severity in subjects who are SARS-CoV-2 seronegative at baseline	2a. Incidence of non-severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS 2b. Incidence of severe COVID-19 disease in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS

	2c. Incidence of deaths due to COVID-19 in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the cellular and humoral immune response to INO-4800	3a. Antigen-specific cellular immune response measured by IFN-gamma ELISpot 3b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay
4. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline	4. Incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seropositive at baseline

3.5 EXPLORATORY OBJECTIVE

See Table 8.

3.6 EXPLORATORY ENDPOINTS

Table 8: Exploratory Objectives and Associated Endpoints

Phase 2 Exploratory Objective	**Phase 2 Exploratory Endpoints**
1. Evaluate the expanded immunological profile of antibody response and T cell immune response	1a. Antigen-specific cellular immune response measured by flow cytometry. 1b. Expanded immunological profile which may include additional assessments of T and B cell numbers and molecular changes by measuring immunologic proteins and mRNA levels of genes of interest as determined by sample availability
Phase 3 Exploratory Objective	**Phase 3 Exploratory Endpoints**
1. Evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease from SARS-CoV-2 variants in subjects who are SARS-CoV-2 seronegative at baseline	1. Incidence of virologically-confirmed COVID-19 disease from a SARS-CoV-2 variant starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (End of Study (EOS)) in subjects who are SARS-CoV-2 seronegative at baseline
2. Evaluate the efficacy of INO-4800 in the prevention of SARS-CoV-2 asymptomatic infection in subjects who are SARS-CoV-2 seronegative at baseline	2. Incidence of SARS-CoV-2 asymptomatic infections in SARS-CoV-2 seronegative subjects starting 14 days after completion of the 2-dose regimen until EOS
3. Evaluate the immunological profile by assessing both antibody response and T cell immune response	3a. SARS-CoV-2 Spike glycoprotein antigen-specific binding antibody levels 3b. Antigen-specific cellular immune response measured by flow cytometry
4. Evaluate antibody persistence	4a. SARS-CoV-2 Spike glycoprotein antigen specific binding antibody levels at Week 30 or later. 4b. Neutralizing antibody response measured by a pseudovirus-based neutralization assay at Week 30 or later

3.7 EFFICACY ASSESSMENT (PHASE 3 SEGMENT ONLY)

Subjects will receive either active investigational product (INO-4800, dose selected from the Phase 2 segment) or placebo (placebo for INO-4800) in a 2-dose regimen administered intradermally followed immediately by EP on Days 0 and 28. Subjects will be monitored through regularly scheduled clinic visits and phone calls throughout the trial. Subjects will be regularly tested for SARS-CoV-2 infection using serologic testing. If COVID-19 disease is suspected based on symptoms or laboratory testing, site personnel will arrange for a clinic visit. Subjects with symptom(s) or a positive SARS-CoV-2 test result will be reviewed by the independent blinded EAC.

The mechanism for review and confirmation of cases will be outlined in an EAC Charter.

3.7.1 CASE DEFINITION FOR VIROLOGICALLY-CONFIRMED COVID-19 DISEASE:

- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with fever (temperature of 100.4ºF/38.0ºC or higher), or
- Positive testing by SARS-CoV-2 RT-PCR assay (performed at central lab*) with any of the following COVID-19 related symptoms:
  - Feeling feverish or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

*Local lab results will be accepted if the subject is hospitalized and a sample is not able to be obtained for analysis at central lab.

3.7.1.1 Case Definition for Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1) with any of the following:
  a. Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg),
  b. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO),
  c. Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors),
  d. Significant acute renal, hepatic, or neurologic dysfunction,
  e. Admission to an ICU, or
  f. Death.

3.7.1.2 Case Definition for Non-Severe COVID-19

- Confirmed COVID-19 disease (per Section 3.7.1);
- Does not meet the case definition of Severe COVID-19 disease (Section 3.7.1.1)

3.7.2 CASE DEFINITION FOR SARS-COV-2 ASYMPTOMATIC INFECTION

Positive testing by SARS-CoV-2 serologic assay (performed at central lab);

- Without clinical signs or symptoms of COVID-19 disease since the previous negative serologic test.

3.8 SAFETY ASSESSMENT

Subjects will be followed for safety during the trial through scheduled clinic visits and phone calls. AEs, regardless of relationship to study drug, will be collected from the time of consent until 28 days post-dose 2 (i.e., Day 56). SAEs, MAAEs and AESIs will be collected from time of consent until EOS. SAEs, AESIs, and treatment-related AEs will be followed to resolution or stabilization. For the Phase 2 segment and at selected sites in the Phase 3 segment, solicited local and systemic AEs will be collected for 7 days following each dose using a participant diary.

Subjects will also be monitored for COVID-19 disease.

Please refer to the Schedule of Events (Table 3 and Table 4) for safety assessments to be performed.

3.9 IMMUNOGENICITY ASSESSMENT

Immunology blood samples will be collected at serial timepoints (see Schedule of Events, Table 3 and Table 4*).* Assays such as binding ELISA, pseudovirus-based neutralization assay, and ELISpot will be evaluated at serial timepoints.

4.0 CLINICAL TRIAL POPULATION

4.1 INCLUSION CRITERIA

4.1.1 PHASE 2 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Assessed by the Investigator to be healthy based on medical history, vital signs and physical examination performed at Screening;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings:
    1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, Transportation Security Administration screening staff, school teachers and college professors teaching in-person classes)
    2. Factory workers (when working in confined settings with large numbers of employees)
    3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft)
    4. User of public transportation (e.g., bus, train, subway) at least 3 times weekly
    5. Nursing home staff or correctional facility staff
    6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas

7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol. Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field)
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, respiratory therapists, physical therapists, social workers, dentists and dental hygienists.) Physicians should not be enrolled unless they are assigned to dedicated COVID-19 treatment wards or other settings with prolonged exposure)
10. Others, if approved by the medical monitor;

f. Screening laboratory results within normal limits for testing laboratory or are deemed not clinically significant by the Investigator;
g. Must meet one of the following criteria with respect to reproductive capacity:
   - Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   - Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 3 months following last dose. Acceptable methods include:
     - hormonal contraception including implants, injections or oral;
     - two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
     - intrauterine device or intrauterine system;
     - abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 PHASE 3 SEGMENT

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. Men and non-pregnant women 18 years of age or older;
c. Per investigator judgment, healthy or stable with pre-existing medical conditions that do not require significant change in medication or have led to a hospitalization in the 3 months prior to enrollment or who, in the judgment of the investigator, are unlikely to require a significant change in therapy or hospitalization for worsening disease through Day 56;
d. Able and willing to comply with all study procedures;
e. Working or residing in an environment with high risk of exposure to SARS-CoV-2 for whom exposure may be relatively prolonged or for whom personal protective equipment (PPE) may be inconsistently used, especially in confined settings. Examples include:
   1. Retail/service workers/educators (restaurant waitresses/waiters and bar workers, street vendors, store cashiers, hairdressers and barbers, veterinary staff, daycare workers, airport screening staff, school teachers and college professors teaching in-person classes, college students attending in-person classes, office workers and volunteers who have multiple brief exposures to people regularly)

2. Factory workers (when working in confined settings with large numbers of employees, meat-packing facilities)
3. Drivers providing bus, taxi or shared ride services (e.g., Uber, Lyft) and delivery services
4. User of public transportation (e.g., bus, train, subway) or public facilities (e.g. gyms) at least 3 times weekly
5. Nursing home staff or correctional facility staff
6. Retirement community residents or adult day program attendees who are regularly eating, socializing and/or exercising in common areas
7. Person 51 years or older living in a multigenerational (at least 3 generations) household
8. First responders (emergency medical technicians, police who are regularly assigned on patrol) Note: Firefighters typically use face shields and other protective gear but may be considered if they regularly assist with medical emergencies in the field
9. Health care workers with prolonged patient interaction (includes nurses and nursing assistants, medical assistants and technicians, respiratory therapists, physical therapists, social workers, dentists and dental hygienists)
10. Others, if in the opinion of the PI, the risk of COVID-19 exposure is comparable to the examples above.

f. Must meet one of the following criteria with respect to reproductive capacity:
   1. Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
   2. Surgically sterile or has a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of vasectomy, subjects should wait six (6) months post-vasectomy prior to enrolling;
   3. Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until last dose. Acceptable methods include:
      i. hormonal contraception including implants, injections or oral;
      ii. two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide);
      iii. intrauterine device or intrauterine system;
      iv. abstinence when this is the subject's preferred and usual lifestyle. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

4.2.1 PHASE 2 SEGMENT

a. Acute febrile illness with temperature > 100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat);
b. Positive serologic or molecular (RT-PCR) test for SARS-CoV-2 at Screening;
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children within the projected duration of the trial starting from the Screening visit until 3 months following the last dose;
d. Positive serum pregnancy test during screening or positive urine pregnancy test immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within the past 3 months;

f. Is currently participating or has participated in a study with an investigational product within 30 days preceding Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous receipt of an investigational vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility).
h. Medical conditions as follows:
   - Respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease) requiring significant changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of hypersensitivity or severe allergic reaction (e.g., anaphylaxis, generalized urticarial or angioedema)
   - Uncontrolled hypertension, defined as resting systolic blood pressure >160 mm Hg or a resting diastolic blood pressure >100 mm Hg prior to first dose;
   - Uncontrolled diabetes mellitus (Hemoglobin A1c > 8.0%);
   - Malignancy within the past 2 years, with the exception of superficial skin cancers that only required local excision and non-metastatic prostate cancer not requiring treatment;
   - Cardiovascular diseases (e.g., myocardial infarction, congestive heart failure, cardiomyopathy or clinically significant arrhythmias) requiring changes in therapy or hospitalization for worsening disease during the 6 weeks prior to enrollment;
   - History of seizures within the past 2 years with the use of no more than a single antiepileptic agent;
i. Immunosuppression as a result of underlying illness or treatment including:
   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the prior 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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);
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
j. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - ICD or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
k. Blood donation or transfusion within 1 month prior to Day 0;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);
m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;

n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.2.2 PHASE 3 SEGMENT

a. Acute febrile illness with temperature ≥100.4°F (38.0°C) or acute onset of upper or lower respiratory tract symptoms (e.g., cough, shortness of breath, sore throat) on Day 0 prior to dosing;
b. Positive serologic test for SARS-CoV-2 at Screening (after approximately 402 subjects positive for SARS-CoV-2 serologic test are randomized, this criterion will apply to all remaining subjects);
c. Pregnant or breastfeeding, or intending to become pregnant or intending to father children starting from the Screening visit until the last dose;
d. Positive urine pregnancy test during screening or immediately prior to dosing;
e. Known history of uncontrolled HIV based on a CD4 count less than 200 cells/mm^3 or a detectable viral load within 3 months prior to screening;
f. Is currently participating or has participated in a study with an investigational product within 30 days prior to Day 0 (documented receipt of placebo in a previous trial would be permissible for trial eligibility);
g. Previous or planned receipt of an investigational (including Emergency Use Authorization (EUA) or local equivalent authorization) or licensed vaccine for prevention or treatment of COVID-19, MERS or SARS (documented receipt of placebo in previous trial would be permissible for trial eligibility);
h. Immunosuppression as a result of underlying illness or treatment including:

   - Primary immunodeficiencies (conditions including hypothyroidism, Hashimoto's thyroiditis and vitiligo are allowed);
   - Long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed) in the past 6 months;
   - Current or anticipated use of disease modifying doses of systemic 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) or others;
   - History of solid organ or bone marrow transplantation;
   - History of or current receipt of any other clinically significant immunosuppressive drugs
   - Diagnosis of an autoimmune disease that may jeopardize the safety of the subject or require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.

i. Lack of acceptable sites for ID injection and EP considering the skin above the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
   - Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
   - Implantable-Cardioverter-Defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
   - Any metal implants or implantable medical device within the electroporation site;
j. Blood donation or transfusion within 1 month prior to Day 0;
k. People who work remotely or in a socially distanced setting with minimal risk of exposure to SARS-CoV-2;
l. Prisoners or subjects who are compulsorily detained (involuntary incarceration);

m. Reported alcohol or substance abuse/dependence or illicit drug use (excluding marijuana use) within the prior 2 years;
n. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL SUBJECTS

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 immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE). If a subject withdraws from the trial or is discontinued from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Day 393) should be performed at the time of discontinuation/withdrawal if the subject agrees. Any related AEs, AESIs, and/or Serious Adverse Events (SAEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.9.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Table 3 and Table 4) following the second dose whether or not the subject has completed both doses.

If a subject decides to be vaccinated with a non-study prophylactic COVID-19 vaccine, either authorized under emergency use or licensed,during the trial, subjects should provide details of the non-study COVID-19 vaccine received to study staff and subjects should be requested to remain in the trial until the last visit. Additionally, subjects should also be advised that we do not have adequate information about the safety and effectiveness of another prophylactic COVID-19 vaccine when received following the receipt of INO-4800. As is already the case, if a subject is enrolled and receives a non-study prophylactic COVID-19 vaccine, either authorized under emergency use or licensed, while on study, the Investigator should enter the details as a concomitant medication. The subject should be followed (according to the Schedule of Events outlined in Table 3 of the Protocol).

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if that fails, then a certified letter to the subject's last known mailing address) so that the subject's disposition can be considered as withdrawn from the study (i.e. lost to follow-up). If the contact with subject is re-established, site should contact medical monitor to discuss whether subject can continue study treatment or follow-up visits for the study. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Reasons for discontinuation/withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time;
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial;
- Investigator, DSMB or Sponsor determines it is in the best interest of the subject;
- Subject non-compliance.

Every effort should be made to obtain information on subjects who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate CRF. However, subjects will not be followed for any reason after consent has been withdrawn. Data and/or samples collected prior to withdrawal of consent will be analyzed.

Reasons for discontinuing subject dosing may include but are not limited to the following:

- Adverse Event (Adverse Reaction);
  - The Investigator or trial coordinator must notify the Sponsor immediately when a subject has been discontinued/withdrawn due to an Adverse Event (AE).
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial;
- Pregnancy.

5.0 CLINICAL TRIAL INVESTIGATIONAL PRODUCT INFORMATION

5.1 INVESTIGATIONAL PRODUCT (IP) AND STUDY DEVICE

5.1.1 INO-4800 AND PLACEBO

Investigational product 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-4800 is the active investigational product to be used in this study. The INO-4800 drug product contains 10 mg/mL of the DNA plasmid pGX9501 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). pGX9501 is a DNA plasmid expressing a synthetic consensus (SynCon®) sequence of the SARS-CoV-2 full length Spike glycoprotein.

Phase 2 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (placebo for INO-4800): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 10-mL glass vials, stoppered, and sealed with aluminum caps.

Phase 3 segment:

Active Investigational Product (INO-4800): A volume of 0.4 mL or 0.8 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps.

Placebo (placebo for INO-4800): Sterile saline sodium citrate (SSC) buffer, which contains sterile 150 mM sodium chloride and 15 mM sodium citrate at a volume of 0.8 mL in 2-mL glass vials, stoppered, and sealed with aluminum caps.

5.1.2 CELLECTRA® 2000

Electroporation is a procedure used to enhance cellular DNA uptake within host cells following DNA vaccine ID delivery. This study will use the CELLECTRA® 2000, a portable, battery-powered medical device designed to generate a controlled, electric field that temporarily and reversibly increases cellular membrane permeability without clinically damaging the tissue. During the period of increased permeability, injected plasmid DNA can be introduced into the cells.

As mentioned above, the CELLECTRA® 2000 device is intended to enhance the uptake and expression of DNA plasmid-based biologics in order to enhance vaccine efficacy. The

DNA plasmid is delivered separately via needle and syringe ID injection immediately prior to the electroporation. The electroporation is accomplished through a sterile, disposable needle Array attached to an Applicator delivering controlled electrical pulses as follows:

- An EP administration consists of four pulses.
- An array of three stainless steel electrode needles is used to deliver the electrical pulses into the tissue. The Array needle length that penetrates into the skin and tissue is approximately 3.2 mm. To date, we have not had any safety concerns associated with the depth of the array electrode needles. Within the Array needle depth of 3.2 mm, there are no major blood vessels (arteries, veins) or nerve structures at the authorized sites of administration overlying the deltoid or the anterolateral quadricep muscle. There are superficial capillaries and minor nerves innervating the skin, including subcutaneous tissues that may be disrupted by needle insertion, but are extremely unlikely to result in serious injury; intradermal injection followed by EP of these structures poses no significant risk to the subject except for possibly injection site reactions.
- The CELLECTRA® 2000 generates four 52ms ±1ms electrical current controlled DC pulses. The nominal current is set to 0.2A ±10% by modulating voltage, or capped at 200V ±5%, determined by patient tissue impedance.
- The total energy delivered by the device is determined by the combination of four device parameters: Pulse Current, Pulse Voltage, Number of Pulses, and Pulse Width. The parameters are pre-set by Inovio to be a pulse current of 0.2A, a pulse voltage of 200V, and 4 pulses at 52ms pulse width. The parameters are verified prior to shipment and cannot be changed by the user.
- In eight clinical trials administering ID injection followed by EP using the CELLECTRA® 2000, total energy delivered ranged from 0.9J to 7.8J, which have been generally safe and well-tolerated. In addition, Inovio has calculated the total maximum energy delivered ID as 8.32J for normal use conditions. Higher energy pulses ranging from 10.7J to 11.7J were evaluated in a guinea pig model which induced erythema localized to the electrode insertion site. Taken together, these nonclinical data and Inovio's clinical experience provide evidence that the total energy delivered by the CELLECTRA® 2000 device will not result in unacceptable risks when delivered to patients. Further, a published study evaluated the Visual Analog Scale (VAS) pain scores of normal use conditions (0.2A), and found ID injection followed by EP using the CELLECTRA® 2000 device to be safe and well tolerated [63].
- The specified current is constantly maintained through voltage modulation using an analog feedback loop. Measurements of voltage and current are processed for error reporting and collected for data logging.

The CELLECTRA® 2000 device is comprised of three components: (1) A battery-powered Pulse Generator, (2) an ID Applicator that is connected to the pulse generator, and (3) a three-point sterile disposable ID Array of stainless steel needles. The Pulse Generator and ID Applicator are reusable components. These components should be cleaned and disinfected prior to each subject's use according to the Cleaning and Maintenance procedure in the User Manual. The Pulse Generator and ID Applicator have been validated for up to 30 cleaning and disinfection cycles based on a maximum of 30 subjects being treated in a day. Therefore, the Pulse Generator and ID Applicator's use should be limited to 30 subjects in a day. Any potential risk of damage to the device due to cleaning

and disinfection for more than 30 cycles has not been validated. Always inspect the device before use according to the instructions in the Maintenance section of the User Manual.

5.2 DOSING REGIMENS

Phase 2 Segment

- Active Investigational Product: One or two 1.0mg ID injection(s) of INO-4800 (~0.1mL dose volume each) followed immediately by EP administered on Day 0 and Day 28 (±3 days)
- Placebo: One or two ID injection(s) of placebo for INO-4800 (~0.1mL) followed immediately by EP administered on Day 0 and Day 28 (±3 days)

Phase 3 Segment

- Active Investigational Product: Two 1.0mg ID injections of INO-4800 (~0.1mL dose volume) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)
- Placebo: Two ID injections of placebo for INO-4800 (~0.1mL) followed immediately by EP administered in separate limbs on Day 0 and Day 28 (±3 days)

5.2.1 BLINDING

This study is blinded. The Sponsor, subjects and clinical site staff, with the exception of the site's pharmacy personnel, will be blinded. There is no difference in appearance between INO-4800 and the placebo; however, they are distinguishable based on the vial size and/or labelling on the vials. In the Phase 2 segment, the vials will be of different sizes and have unblinded labelling. In the Phase 3 segment, the vials will be the same size but will have unblinded labelling. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site.

Under exceptional circumstances, the PI may desire to unblind a subject's dose assignment in case of an emergency or serious medical condition when knowledge of the study product or dose is deemed by the PI to be absolutely essential for proper clinical management of the subject. Under such emergency circumstances, the Sponsor urges the PI to first contact the Medical Monitor (MM) to review options before unblinding the subject's dose assignment. In case of non-emergency, PI must contact MM to discuss the options before unblinding the subject's dose assignment.

The Phase 2 segment of the trial will be unblinded following subjects reaching the Week 30 visit. For the Phase 3 segment, it is not deemed appropriate to unblind a subject's treatment assignment for the purpose of assisting the subject in making a decision regarding receipt a different COVID-19 vaccine (emergency use or licensed vaccine). Subjects may be advised that without efficacy data, INO-4800 has not been proven to be more protective than placebo in the prevention of COVID-19 and SARS-CoV-2 infection. The Sponsor's pharmacovigilance staff may unblind a subject's dose assignment for an SAE, unanticipated adverse device effect (UADE), or adverse event of special interest (AESI) when the event is assessed as related and unexpected. If expedited regulatory reporting is required for such an event, the report may be submitted to regulatory authorities with the subject's dose assignment, in accordance with local regulations.

5.3 PACKAGING AND LABELING

5.3.1 INO-4800 OR PLACEBO

Each vial of INO-4800 or placebo will be labeled consistent with the example product label provided in the IB.

5.3.2 CELLECTRA® 2000

Please see shipping box for shipping documents and contents.

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. Each Pulse Generator has a unique serial number, and each ID Applicator has a unique serial number. Each ID Array has a Lot Number and Expiration Date. Examples of device labels are provided in the IB.

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

5.4 HANDLING AND STORAGE

5.4.1 INO-4800 AND PLACEBO

INO-4800 and Placebo will be shipped at 2–8°C. If the temperature monitoring devices in the shipping container(s) denote temperatures outside this 2–8°C (36-46°F) range, the Sponsor, or its designee, should be contacted immediately.

Upon arrival, the INO-4800 and placebo must be transferred from the shipping container into 2–8°C (36-46°F) storage, in a secure area, in accordance with local regulations by designated personnel (e.g., pharmacy personnel). The Sponsor must be notified of any deviations from this storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly. For further details see Pharmacy Manual and IB.

5.4.2 CELLECTRA® 2000

See User Manual for operating and storage conditions.

5.5 PREPARATION AND DISPENSING

In the Phase 2 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. placebo for INO-4800 is supplied in 10-mL vials at a minimum volume of 2 mL.

In the Phase 3 segment, INO-4800 is supplied in 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 or 0.8 mL. placebo for INO-4800 is supplied in 2-mL vials at a minimum volume of 0.8 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4800 or placebo for INO-4800. Vials will only be handled by designated unblinded personnel (e.g., pharmacy) at the site. When a subject is eligible for enrollment, unblinded personnel will draw INO-4800 or placebo for INO-4800 into a blinded syringe in accordance with the subject's randomized treatment assignment according to a randomization schedule. The syringe will be transferred to blinded site personnel for administration.

Each INO-4800 and placebo vial will contain a volume of product sufficient to dose multiple subjects. The preparation and dispensing information will be provided in the Pharmacy Manual.

5.6 USE OF STUDY DEVICE

The instructions for use of the CELLECTRA® 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA® 2000 device prior to first dose. The EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral injections to patients (e.g., MD, DO, RN) in addition to successfully completing device training provided by Sponsor personnel.

5.7 INVESTIGATIONAL DRUG AND STUDY DEVICE ACCOUNTABILITY

5.7.1 INVESTIGATIONAL PRODUCT (IP) ACCOUNTABILITY

It is the responsibility of the Investigator to ensure that a current accountability record of investigational products (INO-4800 or placebo) is maintained at the study site. The investigational products must have full traceability from the receipt of the products through subject 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

The investigational site is responsible for maintaining device accountability logs. The device must have full traceability from the receipt of the products through subject 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 administration, there must be a record of each product used for that subject, i.e., Pulse Generator serial number, ID Applicator serial number, and ID Array lot number. The ID Applicator is reusable with a new ID Array and sheath for each procedure. The sterile ID Array and sheath are single use only and must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.8 RETURN AND DESTRUCTION OF INVESTIGATIONAL DRUG AND STUDY DEVICE

5.8.1 INO-4800 AND PLACEBO

Upon completion or termination of the study, all unused vials of INO-4800 or placebo must be destroyed at the study site in accordance with institution policy or returned to Inovio Pharmaceuticals, Inc., or its designee if the site cannot destroy IP.

The used vials of INO-4800 and placebo will be discarded in accordance with the 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 in accordance with applicable national, 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 vials should be arranged by the responsible Inovio Representative. The unused IP vials should only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc., personnel or designated Clinical Monitor. If IP vials are returned to Inovio Pharmaceuticals, Inc., or its designee, the IP must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8.2 RETURN OF CELLECTRA® 2000

Upon completion or termination of the study, 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 products 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 products identified above should be arranged by the Inovio Representative. The ID Arrays should be discarded in the sharps container immediately after use. The used ID Applicators can either be destroyed at the site, shipped to a destruction vendor, or returned to Inovio. If the used ID Applicators are 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 in accordance with applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

6.0 CLINICAL TRIAL PROCEDURES AND SCHEDULE

The Schedule of Events (Tables 3 and 4) in the Clinical Protocol Synopsis summarizes the procedures to be performed at each visit. Individual 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 subject 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 trial procedures and the times at which they are to be performed.

6.1.1 CLINICAL TRIAL SCREENING EVALUATIONS

The assessments performed during Screening will determine the subject's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following screening evaluations will be performed for both Phase 2 and Phase 3 segments within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration. Screening and Day 0 visits may be on the same day if eligibility is able to be confirmed prior to randomization. If so, all assessments for Screening and Day 0 must be performed at the combined visit.

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 30-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 clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics;
- Collect socio-behavioral assessment information (Section 6.4);

- Collect AEs (Section 6.4.4);
- Record current concomitant medications/treatments (Section 6.4.6);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Record height and weight (Section 6.4);
- Collect urine for pregnancy test (Section 6.4);
- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect saliva for SARS-CoV-2 RT-PCR (Section 6.4.8).

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, and any other past conditions, as well as surgical procedures, that are considered to be clinically significant by the Investigator and/or having occurred within 3 months prior to Screening. Subjects should be queried about any history of Hepatitis B, Hepatitis C and HIV.

In the Phase 3 segment, subjects with a self-reported history of Hepatitis B or C must provide documentation of liver enzymes that are not significantly elevated within the past 3 months. If such a report of liver enzyme testing is not available, this testing should be performed at Screening. Subjects with a history of Hepatitis C without cirrhosis who have completed treatment and have proof of an undetectable viral load at least 12 weeks following treatment may be enrolled and do not require liver enzymes within the past months.

Subjects with self-reported HIV must provide documentation of controlled HIV infection based on a CD4 count greater than 200 cells/mm^3 or an undetectable viral load within the past 3 months. If a recent CD4 count and/or viral load is not available, this testing should be performed at Screening.

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 Case Report Forms (CRF). Prior treatments, defined as administered up to 12 weeks prior to the time of informed consent and stopped prior to dosing on Day 0, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing on Day 0 or new treatments taken at or after Day 0, should be recorded in the CRF as concomitant medications.

6.1.2 Clinical Trial Evaluations and Procedures

Once eligibility has been confirmed, the subject will be randomized to receive a treatment assignment (INO-4800 or placebo). Visit dates and windows must be calculated from Day 0, unless otherwise noted. All subjects will be followed until the Day 393 Visit. All subjects will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0 and Day 28 (Dosing Visits)

The following evaluations will be performed on **Day 0 and Day 28 prior to dose administration**:

Both Phase 2 and Phase 3 segments:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Obtain any updates to medical history, surgical history (including all clinically significant procedures within the past 12 weeks), present conditions and concomitant illnesses (Day 0 visit only) (Section 6.1.1.1);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4);
- Collect blood for HIV serology (Day 0 visit only) (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Day 0 visit only) (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);
- Review restrictions for injection and EP (Section 6.4.7);
- Randomize subject (instructions to be provided under separate cover) (Day 0 visit only).

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 0 dose (Day 28 visit only).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR (Day 0 only) (Section 6.4.8);
- Collect diary from Day 0 dose during Day 28 visit only(for selected sites only).

The following evaluations will be performed on **Day 0 and Day 28 after IP plus EP administration**:

- Collect any new AEs (Section 6.4.4);
- Download EP Data;
- Provide supplies for subject to use at home, as required (e.g. thermometer, wound guide);
- Phase 2 segment: Distribute diary;
- Phase 3 segment, for selected sites: Distribute diary.

6.1.2.2 Post-dose phone calls

Phase 2 segment: Day 7 and Day 35
Phase 3 segment: Day 14

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);

Phase 2 segment only:

- Review diary (Section 6.4).

Phase 3 segment only:

- Review diary (for selected sites)(Section 6.4);

6.1.2.3 Day 42 Visit

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4);
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only)(Section 6.5);

Phase 2 segment only:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect diary from Day 28 visit.

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect diary from Day 28 visit (for selected sites only);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.4 Phone calls

Phase 2 segment: Day 56
Phase 3 segment: Days 56, 70, 84, 98, 112, 140, 154, 168, 182, 196, 238, 266, 322, 350, and 378

In the Phase 3 segment, phone calls to subjects have been spaced bi-weekly between study visits through Day 210, and approximately monthly between visits from Day 210 to Day 393.

Guidelines for information to be collected during the phone call can be found in the Phone Script. The following evaluations will be performed during the phone call:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Ask about any symptoms of COVID-19 disease; Arrange on-site visit if any signs and symptoms of COVID-19 disease are present (Section 6.4.9);
- Record current concomitant medications/treatments (Section 6.4.6);

6.1.2.5 Follow up clinic visits

Phase 2 segment: Day 210
Phase 3 segment: Days 126, 210 and 294 Visits

Both Phase 2 and Phase 3 segments: The following evaluations will be performed at these visits:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit.
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 Day 201 visit only; Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Ensure subject has necessary supplies at home (e.g. thermometer).

6.1.2.6 Day 393 Visit or EOS

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); SAEs, AESIs, and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Ask about any symptoms of COVID-19 disease;
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 segment:

- Collect blood for CBC with differential and serum chemistry (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Section 6.4.6);
- Collect urine pregnancy test (Section 6.4).

Phase 3 segment:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5).

6.1.2.7 COVID-19 Assessment Visit

For both the Phase 2 and Phase 3 segments of the study, subjects will be evaluated during a COVID-19 assessment visit when acute COVID-19 is suspected based on symptoms or positive SARS-CoV-2 testing. The assessment visit may be performed in the clinic, subject's vehicle, or at a home visit and should be performed within 3 days of a positive SARS-CoV-2 test or site knowledge of COVID-19 symptom onset. The virologic-confirmation of a case will be based on SARS-CoV-2 RT-PCR testing from the central lab. A local RT-PCR result will be considered acceptable in the case where a subject is hospitalized and a sample for central lab analysis is not able to be obtained, if it was obtained using. an assay performed by a laboratory accredited according to standards set by a national or regional accreditation body.

If a local lab is used to confirm the case, the report from the laboratory must be provided.

Phase 2 and Phase 3 segments: The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Optional targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);

Phase 2 only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 only:

- Collect whole blood and serum for cellular and humoral immunology assessment, where possible (Phase 3 cellular immunology collection at selected sites only) (Section 6.5)
- Collect nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (Section 6.4.8).

6.1.2.8 COVID-19 Convalescent Visit

Phase 2 and Phase 3 segments: For subjects with confirmed SARS-CoV-2 infection during the trial, a convalescent visit should be scheduled approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of a positive SARS-CoV-2 test. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization.

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing AEs (Section 6.4.4); Only SAEs, AESIs and MAAEs will be reported after the Day 56 Visit;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.6);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect whole blood and serum for cellular and humoral immunology assessment (Phase 3 cellular immunology collection at selected sites only) (Section 6.5);

Phase 2 segment only:

- Collect nasal swabs and saliva for SARS-CoV-2 RT-PCR detection (Section 6.4.8).

Phase 3 segment only:

- Collect serum for SARS-CoV-2 antibody testing (Section 6.4.8).

6.2 INFORMED CONSENT

All subjects must sign the informed consent prior to participating in any clinical trial-related procedures. The informed consent documentation must be in compliance with applicable regulations and GCP. Qualified clinical trial personnel will:

- Meet with prospective clinical trial subjects;
- Explain the clinical trial;

- Provide clinical trial subjects with an Informed Consent Form (ICF) that includes the following in a language that is understandable to the subject:
  - Screening test(s) description;
  - Eligibility criteria for entering the clinical trial;
  - Clinical trial treatments and follow-up procedures description;
  - Explanation of the clinical trial, including but is not limited to:
    - Clinical trial objectives;
    - Potential benefits and risks;
    - Discomforts/inconveniences;
    - Subject's rights and responsibilities.

The subject is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject. The qualified clinical trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening period.

6.3 ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all clinical trial-related procedures. SIDs are a combination of a site code and a subject number. After SIDs are assigned, they cannot be reused or reassigned for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the CRF.

Previously screen failed subjects may be rescreened provided there is a valid documented reason for rescreening (i.e. changes to the person's health or situation that would make them possibly eligible at this later time). If rescreening occurs, the subject will keep their original Subject ID.

6.4 SAFETY EVALUATIONS

PHYSICAL AND TARGETED PHYSICAL EXAM

A full physical examination will be conducted during Screening and at study discharge/EOS (e.g. Day 393). A targeted physical assessment will be performed at other visits as determined by the Investigator based on subject symptoms.

VITAL SIGNS

Vital signs including temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

At the COVID-19 assessment and convalescent visits, temperature, respiration rate, heart rate and oxygen saturation should be performed.

HEIGHT AND WEIGHT

Weight and height will be collected at Screening.

SOCIO-BEHAVIORAL ASSESSMENT

A Socio-behavioral Assessment, including self-reported smoking and vaping history, and self-reported history of exposure to second-hand smoke will be obtained at Screening.

LABORATORY EVALUATIONS

Blood samples will be collected at visits specified in the Schedule of Events (Tables 3 and 4). A total of approximately mL 245-330mL of blood will be drawn from each subject over the course of the study (inclusive of relevant safety and immunology samples at regular study visits per Tables 3 and 4). If the subject is evaluated at COVID-19 visits, an additional volume of approximately 85-120mL will be collected. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason.

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 (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). Hemoglobin A1c will additionally be performed at Screening (Phase 2 segment only).

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, and total bilirubin (TBili) at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4).

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening (Phase 2 segment only) and at visits specified in the Schedule of Events (Tables 3 and 4). If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

HIV antibody or rapid test will be measured at Day 0 only.

Antibodies to SARS-CoV-2 will be measured at Screening and at visits specified in the Schedule of Events (Tables 3 and 4).

Pregnancy Testing:

Pregnancy testing will be performed on women of childbearing potential (WOCBP). All women will be assumed to be of childbearing potential unless they are:

- Women who are post-menopausal as defined by reported spontaneous amenorrhea for ≥ 12 months;
- Women who are surgically sterile or have a partner who is sterile (i.e., vasectomy in males or tubal ligation, absence of ovaries and/or uterus in females). In the case of a vasectomy, subjects should wait six (6) months post-vasectomy to be considered sterile.

Phase 2: For WOCBP, a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed immediately prior to any dosing and at the subject's last visit.

Phase 3: For WOCBP, a urine pregnancy test will be obtained at Screening and will be performed immediately prior to any dosing.

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 subject is pregnant prior to completing the specified dose regimen, then no further IP

will be administered. Every attempt should be made to follow pregnant subjects for the remainder of the study and to determine the outcome of the pregnancy (see Section 7.12).

DIARY

Diaries will be implemented in the Phase 2 segment of the protocol and at selected sites (estimated to include 711 subjects) in the Phase 3 segment. Subjects will be provided a diary to record the following solicited local and systemic AEs:

- Oral temperature and time taken (each daily entry before 11:59 pm)
- Solicited systemic symptoms
- Solicited local injection site symptoms
- Concomitant medications

The diary should be completed once daily starting the evening of each study dose through 6 days post-dose. The completed diary post-dose 1 and post-dose 2 will be reviewed with the subject by the study staff during the next study phone call or visit and collected at the next in-person study visit. The study staff will review the diary with the subject to assess for temperature, solicited systemic symptoms (unusually tired/feeling unwell, muscle aches, headache, nausea, joint pain) and solicited injection site symptoms (pain, itching, redness, swelling, bruising). In addition, unsolicited symptoms and concomitant medications will be assessed.

Any diary entry determined to meet the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) criteria for a Grade 1 or higher adverse event should be documented as an adverse event unless deemed part of the subject's ongoing medical history. Injection site reactions should be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007 (See Section 6.4.5). If the diary entry does not meet the criteria of a Grade 1 or higher AE as per the relevant guidelines, Investigator clinical judgment can be used to determine whether the entry should be recorded as an AE and documented accordingly in the site's source. For cases where the diary entry and final AE reporting (i.e. grading) do not agree, the reasoning should be recorded in the source documents.

6.4.1 INTRADERMAL INJECTION AND EP

Phase 2 and Phase 3 segments:

A complete administration procedure is defined as an ID injection (formation of a wheal) of IP followed by insertion of the ID Array needles (electrodes) through the skin and into the wheal followed by delivery of four electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug.

Only if the deltoid area is not a suitable location for administration (see exclusion criterion 'j'), the ID injection can then be administered above the lateral quadriceps followed immediately by EP. IP must not be given within 2 cm of a tattoo, scar, keloid, or active lesion/rash. Also, ID injection followed immediately by EP must not be performed on the skin of an extremity which has any metal implants or implantable medical device (e.g., surgical rods, pins or joint replacements). If a subject has an implanted cardiac defibrillator or pacemaker, ID injection/EP must not be performed above the deltoid muscle on the same side of the body where the device is located.

There are three steps that must be performed as part of the administration procedure:

1. Injection of IP (INO-4800 or placebo)
2. Insertion of the array into the subject's skin

3. Pressing the trigger button on the EP applicator

Table 9 below is provided as guidance on how to appropriately complete the procedure when injection of IP has occurred, but the subject did not receive EP.

Table 9: Guidance for how to manage an incomplete administration after IP has been injected

Was IP injected?	Was the array inserted into skin?	Was trigger button pressed?	Action
Yes	Yes (if array gets dislodged before the trigger button is pressed, the same array may be re-inserted)	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	Yes	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure
Yes	No	No	If the drug injection wheal is discernable, EP should be attempted at the site of drug injection to complete the procedure

Reinjection of IP (i.e. protocol-specified IP has already been delivered) is not permitted. Delivery of a second electroporation in tissue is not permitted.

Training will be provided by the Sponsor on use of the device.

Phase 2 segment:

Subjects will receive a two-dose regimen of one or two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection and subsequently followed immediately by EP of each injection site with CELLECTRA® 2000 at Day 0 and Day 28. For subjects assigned to receive two injections + EP at each dosing visit, the two injections must be performed in acceptable locations on two different limbs.

Phase 3 segment:

Subjects will receive a two-dose regimen of two 1.0 mg ID injections of INO-4800 or placebo in a volume of ~0.1 mL in an acceptable skin location for injection on different limbs and subsequently followed immediately by EP of the injection site with CELLECTRA® 2000 at Day 0 and Day 28.

6.4.2 MANAGEMENT OF PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

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

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

6.4.3 ASSESSMENT OF LABORATORY ABNORMALITIES

In Phase 2, samples will be collected for serum chemistry, hematology, and urinalysis at the visits listed in the Schedule of Events (Tables 3 and 4) and as listed in Section 6.4.

Laboratory AEs will be assessed and graded in accordance with 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 AEs.

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

Subjects will be queried regarding the occurrence of any AEs including AEs related to injection site reactions, concomitant medications and new onset illness or disease during their study visits and phone calls. Subjects will be reminded to contact study personnel and immediately report any event for the duration of the study. All AEs will be captured from the time of the informed consent until 28 days post-dose 2 (Day 56). Following the Day 56 visit, only SAEs, AESIs and MAAEs will be collected. All related AEs, AESIs and SAEs will be followed to resolution or stabilization. These events will be recorded on the subject's CRF.

6.4.5 ASSESSMENT OF INJECTION SITE REACTIONS

Reactions arising from the IP administration procedure may be reported as administration site or injection site reactions. When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 10 below) and using the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. All subjects will be observed for 30 minutes following the IP administration procedure for immediate AEs. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions.

Table 10: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

	interference w/ activity			

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

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

[b] Should be evaluated and graded using the functional scale as well as the actual measurement.

6.4.6 CONCOMITANT MEDICATIONS/TREATMENTS

All medications (prescription and nonprescription, including receipt of any non-study COVID-19 vaccine (authorized under emergency use or licensed)) taken between informed consent and study discharge (see Section 4.2) must be recorded on the CRFs.

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and/or any available medical records. The indication for the medication, dose, and dose regimen will be documented.

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator or medical provider. If the permissibility of a specific medication/treatment is in question, please contact the Medical Monitor.

The decision to administer a prohibited medication/treatment (Section 6.4.7) is made with the safety of the clinical trial subject as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

6.4.7 RESTRICTIONS

In the Phase 2 segment of the trial, subjects should refrain from becoming pregnant until 3 months following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1.1). In the Phase 3 segment of the trial, subjects should refrain from becoming pregnant until receipt of the last dose of investigation product by using appropriate contraceptive measures (See Section 4.1).

Subjects must not receive any non-study related vaccine (e.g., influenza vaccine) within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

Subjects must not have fever (oral temperature ≥38.0 degrees Celsius or 100.4° Fahrenheit) within 72 hours prior to each dosing.

Subjects should not receive hydroxychloroquine during the trial. In the Phase 3 segment, subjects should not receive any other drug/vaccine intended as COVID-19 prophylaxis during the trial. Subjects should be reminded that if and when appropriate, the Sponsor would offer INO-4800 to those who received placebo in the trial if INO-4800 is demonstrated to be efficacious.

For subjects in the Phase 2 segment of the trial, the receipt of any non-study prophylactic COVID-19 vaccine (authorized under emergency use or licensed) is not restricted, based upon increasing availability of EUA vaccine in the US and completion of the Phase 3 dose selection from the Phase 2 data.

If a subject informs the site of their intent to receive a non-study prophylactic COVID-19 vaccine available either authorized under emergency use or when licensed, the subject should be informed that the safety and effectiveness of receiving INO-4800 followed by another COVID-19 vaccine has not been studied.

Subjects should not participate in any other interventional trials for the duration of this trial.

Subjects must not receive disease modifying doses of anti-rheumatic drugs (e.g., azathioprine, cyclophosphamide, cyclosporine, methotrexate), biologic disease modifying drugs such as TNF-α inhibitors (e.g., infliximab, adalimumab or etanercept) and long term use (≥7 days) of oral or parenteral glucocorticoids at a dose of ≥20 mg/day of prednisone equivalent (use of inhaled, topical, nasal, otic, and ophthalmic corticosteroids are allowed).

6.4.8 SARS-CoV-2 Testing

Phase 2 segment:

SARS-CoV-2 antibody and RT-PCR testing will be used during screening to test for previous or current SARS-CoV-2 infection. During the trial, subjects who report symptoms suggestive of COVID-19 will be assessed at a COVID-19 assessment visit in the clinic or subject's vehicle or at the subject's home. During this visit, nasal swabs and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed. If the subject is confirmed to be COVID-19 positive, a follow-up nasal swab and saliva will be collected to detect SARS-CoV-2 using the RT-PCR assay at the COVID-19 convalescent visit.

Phase 3 segment:

SARS-CoV-2 antibody testing will be used during screening to test for previous SARS-CoV-2 infection and during each subsequent visit (see Table 4: Schedule of Events) to identify SARS-CoV-2 infections that may occur regardless of symptoms between study visits.

SARS-CoV-2 RT-PCR testing will be conducted on nasopharyngeal specimens collected at Day 0. The Day 0 SARS-CoV-2 RT-PCR results will not be required prior to dosing on that day.

For subjects who are seronegative at baseline, if at any time during the trial, either the SARS-CoV-2 antibody or an RT-PCR test result is positive, the subject will be notified of the result and will be evaluated at a COVID-19 assessment visit. During that visit, which may be conducted in the clinic, from the subject's vehicle, or in the subject's home, nasopharyngeal swabs will be collected to detect SARS-CoV-2 using the RT-PCR assay. Genotyping may also be performed on the sample(s) collected at the COVID-19 assessment visit.

6.4.9 COVID-19 Disease Monitoring

During both the Phase 2 and Phase 3 segments of the trial, all subjects will be monitored for the development of symptoms suggestive of COVID-19 disease. For the Phase 3 segment, frequent (approximately bi-weekly) scheduled clinic visits or phone calls will occur.

All subjects in the trial should be instructed to do the following:

- Take their temperature daily at home starting on the Day 0 visit for the duration of the trial.
- Monitor for symptoms suggestive of COVID-19 (e.g., feeling feverish or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches,

headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea) starting on the Day 0 visit for the duration of the trial.

If at any time during the study, the subject experiences a fever of ≥ 100.4°F/38°C or symptoms suggestive of COVID-19, the subject should contact the site. The site staff should arrange for a clinic visit (COVID-19 assessment visit) within 3 days of the site being aware of either a positive SARS-CoV-2 test or COVID-19 symptom onset. The COVID-19 assessment visit may be performed either at the clinic, in the subject's vehicle or in the subject's home.

Subjects with a confirmed COVID-19 diagnosis, per the case definition outlined in Section 3.7, prior to dose 2 or who have a positive SARS-CoV-2 PCR test at Day 0 will be discontinued from further dosing and will be followed until EOS for safety and resolution of COVID-19. Subjects with confirmed SARS-CoV-2 infection will return for a convalescent visit approximately 28 days after symptom onset, or in the absence of symptoms, after the collection date of the positive SARS-CoV-2 sample. If symptoms are ongoing at 28 days after symptom onset, the site should follow up with the subject via phone call or unscheduled visit after symptom resolution or stabilization. Recovery from COVID-19 disease requires either resolution of clinical symptoms except for loss of taste/smell, or with sequelae that appear to be permanent.

Subjects who require medical care for COVID-19 (or any other suspected condition) will be referred to their primary health care provider or a medical treatment facility if the Investigator believes that the subject should be managed beyond routine care that can be provided by the study site. Subjects referred for treatment will continue study follow-up according to the protocol schedule. If subjects are treated or hospitalized due to their illness, the study team will request COVID-19 specific test results, treatments, treatment outcomes and diagnostics from medical treatment facilities with the subject's written permission. These results and diagnostics will be recorded in the study and/or safety database consistent with protocol reporting requirements.

6.5 IMMUNOGENICITY ASSESSMENTS

Whole blood and serum samples will be obtained at visits specified in the Schedule of Events (Tables 3 and 4) for cellular and humoral immunology assessments. Binding ELISA will be evaluated at serial timepoints. Cellular sampling requires 32 mL of whole blood be collected at each visit. Humoral sampling requires collection of 8.5 mL of whole blood in a single 10-mL red top serum collection tube to produce two serum aliquots of 2 mL each. However, baseline (Day 0) immunology samples are required to serve as a baseline for all subsequent immunology testing. Therefore, a total of 68 mL whole blood for cellular sampling and 8 mL serum for humoral sampling is required on Day 0 prior to 1st dose. Subjects may be asked to return for additional blood draws if collected blood sample is lost or unevaluable for any reason. Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

Humoral samples will be collected on all subjects and cellular samples will be collected at selected sites (from approximately 711 subjects). Both humoral and cellular analysis will be conducted in the first 102 subjects age 18-50 and in the first 102 subjects age 51 and older enrolled at the sites that are selected for cellular sample collection. In addition, cellular and humoral samples will be analyzed on all subjects with COVID-19 when samples are available.

The immune responses to INO-4800 will be measured using assays that include a pseudovirus-based neutralization assay and ELISpot. Determination of additional analyses using assays not specified, such as assessment of immunological gene

expression or flow cytometry, assessment of immunological protein expression on collected samples for immunological endpoints will be made on an ongoing basis throughout the trial.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4800 will be measured and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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 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 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).

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;
- 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;
- Confirmed COVID-19 disease.

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 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;
- Confirmed COVID-19 disease that requires hospitalization is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- COVID-19 disease with an outcome of death is recorded on the Suspected COVID-19 Clinical Event CRF, and not recorded as an SAE;
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event;
- Complications associated with COVID-19 disease that occur or prolong hospitalization are recorded on the Suspected COVID-19 Clinical Event CRF;
- The Pregnancy outcomes of spontaneous abortion (miscarriage), ectopic pregnancy, fetal demise/stillbirth in a subject or subject partner following exposure to study treatment is considered to be 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.

7.7 DEVICE DEFICIENCY

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

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 AEs classified by system organ class, preferred term, severity and causal relationship to clinical trial treatment;
- Changes in laboratory parameters;
- Local and systemic injection site review; special attention will be paid to the examination of the injection site.

7.8.1 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

For the purpose of this clinical trial, the AESIs listed in Appendix A are to be reported to the Sponsor in accordance with Section 7.9.

7.8.2 MEDICALLY ATTENDED ADVERSE EVENT (MAAE)

A medically attended adverse event (serious or non-serious) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.8.3 ABNORMAL LABORATORY VALUE

The Investigator will annotate each abnormal lab value as clinically significant (CS) or not clinically significant (NCS).

Laboratory values that are NCS in the Investigator'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 further administration of the investigational product in the clinical trial;
- Has accompanying or inducing symptoms or signs;
- Is judged by the Investigator 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.

7.8.4 CLINICAL TRIAL STOPPING RULES

The Investigator is to immediately notify the Medical Monitor if the following are observed:

- Any SAE related to study treatment (i.e., IP and/or the study device);
- Any Grade 4 AEs related to study treatment (i.e., IP and/or the study device);
- Any report of anaphylaxis related to study treatment (i.e., IP and/or the study device);
- Any suspected Severe COVID-19 disease case (per Sections 3.7.1.1 and Section 3.7.1.2).

The Medical Monitor will notify the Chair of the Safety Review Committee, who will make a determination as to whether to temporarily halt dosing until a more formal review of the case(s) is made. Such a formal review may include an ad hoc meeting of the DSMB, after consultation with the DSMB Chair. Following such a meeting, the DSMB chair will render a recommendation to the Medical Monitor regarding continuation of trial dosing. The Sponsor will independently investigate the case(s) and, after review of the DSMB recommendations, will communicate a final decision as to whether to lift the dosing suspension or whether to continue dosing. These deliberations will be documented and will be provided to the IRBs and FDA, where required.

In the case of suspected Severe COVID-19 cases, the trial will be paused if a vaccine-to-placebo case split yields a relative risk with a 90% confidence interval lower bound >1. The minimum case split corresponding to this criterion is 8:0. In this scenario, the trial will pause until at least one additional case is accrued and the DSMB can review the data and make a recommendation regarding continued enrollment in the trial.

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained through Day 56. MAAEs, AESIs and SAEs only will continue to be collected after the Day 56 visit and will be followed to resolution or stabilization. This information will be captured in the CRF.

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

SAEs and AESIs will be reported to the Sponsor from the time the subject signs the informed consent until the last visit.

All SAEs (regardless of causal relationship) and AESIs will be reported on the SAE Report Form and submitted to the Sponsor within 24 hours of becoming aware of the event. The SAE Report Form will be either emailed to safety.inovio@apcerls.com or faxed to [redacted] The original SAE Report Form must be kept at the clinical trial site.

The event will be data entered into the CRF.

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

Table 11: SAE Contact Information

Sponsor Safety Email: safety.inovio@apcerls.com
Sponsor Safety Fax: [redacted]
Sponsor Safety Phone: [redacted]

Table 12: Medical Monitor Direct Contact Information

Primary point of contact, ICON Medical Monitor: [redacted] M.D.
Email: [redacted]
Phone: [redacted]
Inovio Medical Monitor: [redacted], Jr., M.D., FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

All SAEs, treatment-related AEs, MAAEs and AESIs must be followed by the Investigator until resolution or return to baseline status, stabilization of the event (i.e., the expectation that it will remain chronic), even if it extends beyond the clinical trial reporting period or until it is determined that the subject is lost to follow up.

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 subject's assigned identification 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 Investigator 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 number (SID);
- Investigational product(s) (IP) and/or study device;
- Investigator causal relationship to the IP(s) and/or study 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

Investigators should use correct medical terminology/concepts when recording AEs on the EDC and SAE 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 previous signs and/or symptoms will be subsumed 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 Investigator will assess and grade clinical AEs or SAEs (based on discussions with clinical trial subjects) in accordance with CTCAE.

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 Investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject’s response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator 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.

Investigators 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 Investigator 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 Investigator'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 SUSPECTED COVID-19 DISEASE CASES DURING THE TRIAL

For both Phase 2 and Phase 3 segments of the trial, all suspected COVID-19 disease cases based on reported COVID-19 symptoms and/or SARS-CoV-2 test results should be entered into the Suspected COVID-19 Clinical Event CRF within 24 hours of awareness. Cases will be tracked until final determination of whether the case meets criteria of a confirmed COVID-19 disease case, per the case definition. For the Phase 2 segment of the trial, this determination will be made by the Investigator. For the Phase 3 segment, this determination will be made by the EAC.

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if serious, would be reported as an SAE within 24 hours following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

If the reported COVID-19 disease case is later determined not to be a confirmed COVID-19 case, the event (e.g. symptoms or other diagnosis), if non-serious and if occurring from the time of consent until 28 days post-dose 2, would be reported as an AE following determination by the Investigator (Phase 2 segment) or notification by EAC (Phase 3 segment).

7.12 REPORTING PREGNANCY DURING THE CLINICAL TRIAL

Subjects in Phase 2 who are pregnant or expect to become pregnant prior to 3 months following the last dose will be excluded from participation in the clinical trial.

Subjects in Phase 3 who are pregnant or expect to become pregnant prior to the last dose will be excluded from participation in the clinical trial.

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (i.e., Day 393) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after the first dose in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

The Investigator 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 dose administrations, must not be performed. The Investigator 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 Investigator if their partner becomes pregnant until study completion. A Pregnancy Form will be completed by the site and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy. The pregnant partner will be asked to sign a Pregnancy Information Collection Consent Form to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator will collect and report details of the course and outcome of the pregnancy in the partner of a male subject exposed to IP. The site will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and submit the form to the Sponsor.

If an Investigator is contacted by the male subject or his pregnant partner, the Investigator 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.

7.13 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 clinicalcomplaint@inovio.com.

Device deficiencies include malfunctions, misuse or 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 or marketed.

Any problems experienced during the treatment procedure including malfunctions of the device (e.g. significant device malfunction causing injury or resulting in a hazard which could cause injury to the subject or user), 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. The Sponsor will review these reports for potential hazards that could cause an SAE. If Inovio determines that the malfunction could cause an SAE, the Inovio Medical Monitor will decide whether the Chair of the Safety Review Committee should be notified in accordance with Section 7.8.4.

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

7.14.1 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.

7.14.2 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, and AESIs) that occur at their clinical trial site in accordance with their local institutional policy.

7.15 POST-TRIAL REPORTING REQUIREMENTS

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 related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor.

7.16 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at a 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, INOVIO, 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, all IP and devices must be returned to INOVIO or its representative. The PI should ensure that their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8.0 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL AND ANALYTICAL PLAN

The formal 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 an operationally seamless Phase 2/3 trial. The subjects and data from Phase 2 are independent from that of Phase 3.

Phase 2 Segment: This is a four-arm, multi-center, placebo-controlled, blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The trial's primary endpoints are antigen-specific cellular immune response measured by IFN-gamma ELISpot and neutralizing antibody responses. Secondary efficacy endpoints are safety measures. Exploratory endpoints are antigen-specific cellular immune response measured by flow cytometry and other T and B cell measures.

Phase 3 Segment: This is a two-arm, multi-center, placebo-controlled, double-blinded, and randomized clinical trial in subjects at high risk of SARS-CoV-2 exposure. The study's

primary endpoint is the incidence of virologically-confirmed COVID-19 disease in subjects who are SARS-CoV-2 seronegative at baseline starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2. The primary hypothesis is that INO-4800 will be efficacious relative to placebo (relative efficacy > 30%). Secondary efficacy analyses involve non-severe cases, severe cases, cases resulting in death, and cases among baseline SARS-CoV-2 seropositive subjects. Other secondary analyses concern safety and cellular and neutralizing antibody response. Exploratory analyses concern efficacy against variants, efficacy against asymptomatic infection, and binding antibody and cellular immunological measures.

8.3 STATISTICAL HYPOTHESES

Phase 2 Segment: This is an estimation segment pertaining to immunogenicity and safety. There are no hypotheses.

Phase 3 Segment: The primary hypothesis of relative efficacy greater than 30% among baseline SARS-CoV-2 seronegative subjects will be tested with H_0: $p \geq .70/(.70+k)$ *vs.* H_1: $p < .70/(.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group. There are no other formal hypotheses.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The per-protocol (PP) population includes all subjects who receive all doses of Study Treatments and have no protocol violations. Subjects in the PP population will be grouped to treatment arms as randomized. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database. Analyses on the PP population among those who are baseline SARS-CoV-2 seronegative will be primary for the analyses of efficacy in the Phase 3 segment of this trial.

The modified intention to treat (mITT) population includes all subjects who receive at least one dose of Study Treatment. Subjects in this population will be grouped to treatment arms as randomized. Analysis of the mITT population will be considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

The intention 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 considered supportive for the corresponding PP population for the analyses of efficacy in the Phase 3 segment of this trial.

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

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY ANALYSIS

Phase 2 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects. Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

Phase 3 Segment

Among subjects who are SARS-CoV-2 seronegative at baseline, the primary hypothesis of relative efficacy greater than 30% will be tested with H_0: $p \geq 0.70/(0.70+k)$ *vs.* H_1: $p < 0.70/(0.70+k)$, where p is the true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease, and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the INO-4800 group.

A p-value for this hypothesis test and corresponding confidence interval will be computed based on the exact binomial method of Clopper-Pearson. Success will be concluded if the one-sided p-value is <0.022 and the corresponding lower bound of the two-sided 95.6% CI for efficacy exceeds 30% (alpha-level adjusted for interim analyses, see Section 8.5.6), and the point estimate for efficacy exceeds 50%.

For calculating k, an individual subject's follow-up time is either:

- the date of first disease diagnosis – date of the start of surveillance period +1 (for subjects who are cases), or
- the date of last follow-up – date of the start of surveillance period +1 (for subjects who are non-cases).

This methodology is based on the following. Assuming that the number of subjects who are cases in the INO-4800 group follows a Poisson distribution with parameter λ_v and the number of subjects who are cases in the placebo group follows a Poisson distribution with parameter λ_c, then conditional on total number of subjects with cases, t, the number of subjects who are cases in the INO-4800 group follows a binomial distribution with parameters $(t, p=\lambda_v/(\lambda_v+\lambda_c))$. The relationship between p and efficacy is: efficacy = $(1-(1+k)p)/(1-p)$. Therefore, testing efficacy > 30% corresponds to testing $p < 0.70/(0.70+k)$. Similarly, the confidence interval for efficacy is $(1-(1+k)UB_p)/(1-UB_p)$, $(1-(1+k)LB_p)/(1-LB_p)$, where UB and LB are the Clopper-Pearson upper and lower limits for the proportion.

The efficacy time frame is defined by symptoms beginning at any time starting from 14 days after Dose 2 and ending 12 months after Dose 2. Subjects identified as cases that started prior to this time point will be excluded. Subjects with multiple instances meeting the case definition will be counted only once, using the first such instance.

The PP population will be primary for the analysis of efficacy in this trial. Efficacy analysis using the mITT population will also be conducted counting cases from 14 days postdose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

8.5.2 SECONDARY ANALYSES

8.5.2.1 Efficacy

Phase 3 Segment

The secondary efficacy incidence endpoints will be analyzed in the same manner as the primary hypothesis, but with 95% CIs and without the hypothesis test p-value.

8.5.2.2 Immunogenicity

Phase 3 Segment

Post-baseline increases from baseline in interferon-γ ELISpot response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects and by baseline SARS-CoV-2 serostatus.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint.. Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for these immunogenicity analyses.

8.5.3 **SAFETY ANALYSES**

8.5.3.1 Adverse Events

All AEs including injection-site reactions will be summarized among the Safety Population by frequency per treatment arm. These frequencies will be presented overall and separately by dose, and will depict 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 AEs will also be summarized as above.

The main summary of safety data will be based on events occurring within 30 days of any dose. For this summary, the frequency of preferred term events will be compared between study arms with risk differences and 95% confidence intervals, using the method of Miettinen and Nurminen. As this analysis will use many event categories, and produce many confidence intervals, caution should be exercised when interpreting these confidence intervals. Separate summaries will be based on events occurring within 7 days of any dose and regardless of when they occurred.

The analyses listed above will be performed according to the Phase of the trial. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

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.

8.5.3.2 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 and treatment arm, for the Safety population. Baseline is defined as the last measurement prior to the first treatment administration. These summaries will be performed according to Phase. For the Phase 2 segment, the analyses listed above will also be performed according to prior receipt of any non-study prophylactic COVID-19 vaccine. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.4 DISPOSITION

Disposition will be summarized by treatment arm for the ITT population and will include the number and percentage randomized, 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. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.5.5.1 Demographics

Demographic data will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.5.2 Prior Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.5.6 INTERIM ANALYSES

For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose. The two-sided type I error of 0.05 will not be adjusted for possible early stopping due to this aspect.

For the Phase 2 segment, group-level unblinded summaries of the immunogenicity and safety data will be produced once Week 6 visit immunology data and Week 8 visit safety

data are complete for all subjects who have not discontinued, while maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all subjects who have not discontinued with remaining visits through the final visit. These summaries will allow the Sponsor to have results for the purposes of dose selection for the Phase 3 portion. No subject-level immunogenicity data will be produced, and subject-level immunogenicity data will not be available in the clinical trial database until all other clinical trial data are finalized at the end of the trial. No safety summary will be provided if the total number of subjects who experience the event of interest is greater than 0 and the count of the number of subjects with the event in a given treatment group relative to the total produces a percentage less than 3%, for a given summary. The group-level unblinded production of the summaries will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

For the Phase 3 segment, there are two planned formal interim efficacy analyses: one at 50% (75 cases) and one at 75% (112 cases) of the total required for the primary endpoint (149 cases). The Lan-DeMets O'Brien-Fleming approximate alpha-spending function will be used for the efficacy and futility boundaries. As such, the first interim analysis will utilize a one-sided nominal alpha of 0.0016, and the second interim analysis will utilize a one-sided nominal alpha of 0.0092. The final analysis will utilize a one-sided nominal alpha of 0.022. The DSMB will be responsible for the interim evaluations. The unblinded interim analyses will not include anyone directly involved with the trial or any additional unblinded personnel; only the external Contract Research Organization (CRO), ICON, which will already be providing unblinded summaries for the Data Safety Monitoring Board, will be utilized. Thus, the trial will remain blinded to the Sponsor with respect to subject treatment assignment.

If the prespecified criteria for efficacy above are met at either interim analysis, then enrollment will continue until 4500 subjects have been enrolled, and blinded follow-up will continue until 4500 subjects have 6 months of safety follow-up. At that point, the trial would be unblinded, and subjects who received placebo will be offered the active product.

8.5.7 MULTIPLICITY

There is one primary hypothesis that will be tested. As there are two interim analyses of the primary endpoint, the type I error rate will be controlled at two-sided 0.05 by using the Lan-DeMets O'Brien-Fleming approximate alpha-spending function (see Section 8.5.6).

8.5.8 MISSING VALUES

Missing data will not be imputed.

For the ITT analyses of efficacy in the Phase 3 segment, subjects with missing or unevaluable data regarding case definition will be considered cases (failures).

8.5.9 EXPLORATORY ANALYSES

8.5.9.1 Efficacy

Phase 3 segment

The exploratory efficacy endpoints will be analyzed in the same manner as the primary hypothesis, but with a 95% CI and without the hypothesis test p-value.

8.5.9.2 Immunogenicity

Phase 2 segment

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

The summaries listed above will be stratified according to NP positive/negative status and according to prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

Phase 3 Segment

Post-baseline increases in antibody titers from ELISA will be compared between treatment groups using ratios of geometric mean fold-rises and associated 95% t-distribution based CIs.

Post-baseline increases from baseline in cellular response magnitudes will be compared between treatment groups using differences in medians and associated non-parametric 95% CIs.

Post-baseline increases from baseline in neutralizing antibody response titers will be compared between treatment groups using ratios of geometric mean fold-rises and associated t-distribution based 95% CIs.

The summaries listed above will be stratified according to disease status of the subjects.

Valid samples for statistical analysis purposes will be those collected: at least 6 and no more than 30 days after Dose 2 for the Week 6 timepoint; at least 174 and no more than 198 days after Dose 2 for the Week 30 timepoint; and at least 356 and no more than 380 days after Dose 2 for the Week 56 timepoint. . Baseline is defined as the last measurement prior to the first treatment administration.

The PP population will be used for immunogenicity analyses.

8.5.9.3 Concomitant Medications

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 by treatment arm, for the ITT and PP populations. These summaries will be performed according to Phase. For the Phase 3 segment, the analyses listed above will also be performed according to SARS-CoV-2 serostatus at baseline.

8.6 SAMPLE SIZE/POWER

Phase 3 segment: The trial is case-driven. A total of 149 observed cases among baseline SARS-CoV-2 seronegative subjects will be required to provide 90% power to declare the vaccine efficacious (>30%), assuming a true efficacy of 60% and utilizing the methodology

described in Section 8.5.1 and Section 8.5.6. A sample size of 6714 baseline SARS-CoV-2 seronegative subjects will be required to achieve this number of cases assuming an underlying attack rate of 3.7%.

8.7 RANDOMIZATION AND BLINDING

Phase 2 Segment

Subjects will be randomized (3 INO-4800 1.0 mg, one injection: 3 INO-4800 2.0 mg, two injections:1 Placebo, one injection: 1 Placebo, two injections).

The study is blinded. It is double-blinded within dose group. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups. Subject treatment assignments will be unblinded after Phase 2 subjects have reached the Week 30 visit.

Phase 3 Segment

Subjects will be randomized (2 INO-4800:1 Placebo). Randomization will be stratified according to two factors, each with two levels: a) age-group age category (18-50 years vs. ≥51 years) on Day 0, and b) presence or absence on Day 0 of underlying medical conditions that increase risk of severe COVID-19 disease, per US CDC criteria.

The study is double-blinded. Randomization and blinding will avoid bias in the assignment of subjects to treatment, increase the likelihood that known and unknown subject attributes (e.g., demographics and other baseline characteristics) are evenly balanced between treatment groups, and enable valid statistical comparisons between treatment groups.

9.0 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)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC)

The Investigator will commence the clinical trial after full approval of the protocol and adjunctive materials (e.g., ICF, advertising) has been obtained from the applicable IRB/REB/EC and a copy of IRB/REB/EC approval documentation has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/REB/EC include the following:

- Submit continuing review reports to the IRB/REB/EC as required, and request re-review and approval of the clinical trial at least once a year during the conduct of the clinical trial;
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects;
- Notify the IRB/REB/EC immediately if the Sponsor notifies the Investigator about any reportable safety events;

- Obtain approval from the IRB/REB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required;
- Submit reports on, and reviews of, the clinical trial and its progress to the IRB/REB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines;
- Maintain a file of clinical trial-related information (refer to clinical trial files) that includes all correspondence with the IRB/REB/EC;
- Notify the IRB/REB/EC when the clinical trial is completed (i.e., after the last clinical trial visit of the final clinical trial subject);
- After clinical trial completion (within three [3] months is recommended), provide the IRB/REB/EC with a final report on the clinical trial.

Institutional Biosafety Committee (IBC)

The Investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., pharmacy manual) has been obtained from the applicable IBC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IBC include the following:

- Notify the Sponsor, IBC and NIH OSP within 30 days of any:
  - Substantial problems or violation of the NIH Guidelines
  - Significant research related accidents or illnesses
- Notify the IBC to any changes to the research (dosage, procedure, etc.) or facility (new space, remodeling, etc.).

9.3 PROTECTION OF HUMAN SUBJECTS

9.3.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent must be obtained from each subject prior to the subject's enrollment in the clinical trial. The process for obtaining informed consent must be documented in the subject's medical record (also refer to Section 6.2).

9.3.2 COMPLIANCE WITH INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)/ETHICS COMMITTEE (EC) REQUIREMENTS

This clinical trial is to be conducted in accordance with applicable IRB/REB/EC regulations. The Investigator must obtain approval from a properly constituted IRB/REB/EC prior to initiating the clinical trial and obtain re-approval or review at least annually. The Sponsor is to be notified immediately if the responsible IRB/REB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/REB/EC correspondence with the Investigator should be provided to the 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 (21CFR PART 11)

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

9.3.5 COMPLIANCE WITH PROTOCOL

Subjects are not required to follow special instructions specific to the IP used in this clinical trial. Subjects 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 an important deviation be discovered, the Sponsor must be informed immediately. Any protocol deviation impacting subject 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 Sponsor approval and prior review and documented approval/favorable opinion of the protocol amendment from the IRB/REB/EC, except where necessary to eliminate immediate hazards to clinical trial subjects, or when the changes involve only logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers).

10.0 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 subjects' 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.

11.0 SOURCE DOCUMENTS

Source data is all information, electronic or hardcopy 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.

Examples of original source data records may include:

- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Pharmacy dispensing records
- Recorded data from automated instruments

- Copies of electronic medical records (EMR) certified after verification as being accurate and complete
- 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 INO-4800. 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.

If the Records Retention requirements are addressed in a governing clinical trial agreement, it is the Investigator's responsibility to retain clinical trial essential documents in accordance with the governing clinical trial agreement and applicable local requirements.

12.0 SAFETY AND QUALITY MONITORING

12.1 SAFETY REVIEW

The Sponsor's Safety Review Committee (SRC), composed of the Sponsor's Medical Monitor, the ICON Medical Monitor and 1 additional physician, will review blinded safety and tolerability data on a regular basis throughout the trial. The SRC will refer any of the events listed in Section 7.8.4 or any other safety concerns to the DSMB Chair.

For both the Phase 2 and 3 segments, the Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded safety data, and additionally upon completion of the Week 8 phone call visit for all subjects enrolled during the Phase 2 segment. The DSMB will review unblinded safety and tolerability data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data for all enrolled subjects. The DSMB will also evaluate the data for signals of vaccine-enhanced disease and in the event of a signal, advise whether to halt the trial. The DSMB will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause and trial suspension. For the Phase 3 segment, the DSMB will also review efficacy in an unblinded fashion.

If the safety data is considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination at which time further enrollment and

administration of IP to subjects will be paused. The Sponsor will perform an investigation and consult with the DSMB and other experts, if needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

12.2 CLINICAL MONITORING

Clinical Monitoring will be performed by qualified Clinical Monitors who will report to the Sponsor or the Sponsor's designee. 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 trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/REB/EC policies.
  - Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).
  - Assure that the trial facilities, including the pharmacy, continue to be acceptable.
  - Compare the 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 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.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor of this study. The Department of Defense, Joint Program Executive Office is providing funding for the Phase 2 segment of the study and Inovio is providing funding for the Phase 3 segment. Clinical trial insurance has been taken out according to 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 per ICH E6 R1.

14.0 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.

15.0 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA-C	Attributable, Legible, Contemporaneous, Original, Accurate and Complete
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
COVID-19	Coronavirus Disease 2019
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot-forming assay
EP	Electroporation
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO_3	Biocarbonate
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Implantable-Cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Intradermal
IM	Intramuscular
Inovio	Inovio Pharmaceuticals Inc.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
MAAE	Medically Attended Adverse Event
mITT	modified Intent to Treat
MM	Medical Monitor
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mRNA	Messenger RNA
Na	Sodium
NCS	Not Clinically Significant
NHP	Non-human Primates
NP	Nucleocapsid Protein
PHI	Personal Health Information
PI	Principal Investigator
PII	Personal Identifying Information
PO_4	Potassium

PT	Preferred Term
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus - 2
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TBili	Total Bilirubin
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

16.0 REFERENCES

1. Centers for Disease Control and Prevention. *People with Certain Medical Conditions*. March 29, 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
2. Lu, H., C.W. Stratton, and Y.W. Tang, *Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle.* J Med Virol, 2020. **92**(4): p. 401-402.
3. Hui, D.S., et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China.* Int J Infect Dis, 2020. **91**: p. 264-266.
4. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
5. GenBank. *Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome*. 2020; Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947.
6. Smith, T.R.F., et al., *Immunogenicity of a DNA vaccine candidate for COVID-19.* Nat Commun, 2020. **11**(1): p. 2601.
7. World Health Organization, *Clinical Management of Sever Acute Respiratory Infection When Novel Coronavirus (2016-nCoV) Infection is Suspected. Interim Guidance.* 2020.
8. World Health Organization, *Novel Coronavirus (2019-nCoV) Situation Report*. 2020.
9. Wiersinga, W.J., et al., *Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.* JAMA, 2020.
10. World Health Organization, *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*. March 11, 2020.
11. Zou, L., et al., *SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.* N Engl J Med, 2020.
12. Center for Systems Science and Engineering at Johns Hopkins University, *COVID-19 Dashboard*. 2020.
13. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Intern Med, 2020.
14. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* Chin J Epidemiol, 2020. **41**(Epub ahead of print).
16. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020.* China CDC Weekly, 2020. **2**(8): p. 113-122.
17. Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* Lancet, 2020. **395**(10223): p. 514-523.
18. Rothe, C., et al., *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany.* N Engl J Med, 2020. **382**(10): p. 970-971.
19. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020.* Euro Surveill, 2020. **25**(17).
20. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020. **26**(5): p. 672-675.

21. Liu, Y., et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus.* J Travel Med, 2020. **27**(2).
22. Centers for Disease Control and Prevention. *Symptoms of Coronavirus*. 2020 March 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
23. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* N Engl J Med, 2020.
24. Day, M., *Covid-19: four fifths of cases are asymptomatic, China figures indicate.* BMJ, 2020. **369**: p. m1375.
25. Centers for Disease Control and Prevention. *COVID-19 Pandemic Planning Scenarios*. July 10, 2020 July 20, 2020 July 27, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
26. Lipsitch, M., et al., *Transmission dynamics and control of severe acute respiratory syndrome.* Science, 2003. **300**(5627): p. 1966-70.
27. Peiris, J.S., et al., *Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.* Lancet, 2003. **361**(9371): p. 1767-72.
28. Tsang, T.K., et al., *Influenza A Virus Shedding and Infectivity in Households.* J Infect Dis, 2015. **212**(9): p. 1420-8.
29. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
30. Long, Q.X., et al., *Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.* Nat Med, 2020.
31. Diao, B., et al., *Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19).* Front Immunol, 2020. **11**: p. 827.
32. Grifoni, A., et al., *Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals.* Cell, 2020. **181**(7): p. 1489-1501 e15.
33. Modjarrad, K., et al., *Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial.* Lancet Infect Dis, 2019. **19**(9): p. 1013-1022.
34. Suschak, J.J., J.A. Williams, and C.S. Schmaljohn, *Advancements in DNA vaccine vectors, non-mechanical delivery methods, and molecular adjuvants to increase immunogenicity.* Hum Vaccin Immunother, 2017. **13**(12): p. 2837-2848.
35. Manickan, E., K.L. Karem, and B.T. Rouse, *DNA Vaccines - A Modern Gimmick or a Boon to Vaccinology?* Crit Rev Immunol, 2017. **37**(2-6): p. 483-498.
36. Porter, K.R. and K. Raviprakash, *DNA Vaccine Delivery and Improved Immunogenicity.* Curr Issues Mol Biol, 2017. **22**: p. 129-138.
37. Li, L. and N. Petrovsky, *Molecular mechanisms for enhanced DNA vaccine immunogenicity.* Expert Rev Vaccines, 2016. **15**(3): p. 313-29.
38. Marc, M.A., E. Dominguez-Alvarez, and C. Gamazo, *Nucleic acid vaccination strategies against infectious diseases.* Expert Opin Drug Deliv, 2015. **12**(12): p. 1851-65.
39. Grunwald, T. and S. Ulbert, *Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases.* Clin Exp Vaccine Res, 2015. **4**(1): p. 1-10.
40. Tregoning, J.S. and E. Kinnear, *Using Plasmids as DNA Vaccines for Infectious Diseases.* Microbiol Spectr, 2014. **2**(6).
41. Williams, J.A., *Improving DNA vaccine performance through vector design.* Curr Gene Ther, 2014. **14**(3): p. 170-89.
42. Liu, M.A., *DNA vaccines: an historical perspective and view to the future.* Immunol Rev, 2011. **239**(1): p. 62-84.

43. Wahren, B. and M.A. Liu, *DNA Vaccines: Recent Developments and the Future.* Vaccines (Basel), 2014. **2**(4): p. 785-796wahren.
44. Ledgerwood, J.E. and B.S. Graham, *DNA vaccines: a safe and efficient platform technology for responding to emerging infectious diseases.* Hum Vaccin, 2009. **5**(9): p. 623-6.
45. Keefer, M.C., et al., *Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV type 1-seronegative humans. The AIDS Vaccine Clinical Trials Network.* AIDS Res Hum Retroviruses, 1994. **10**(12): p. 1713-23.
46. Wu, F., et al., *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.* Medrxiv Preprint, 2020.
47. Martin, J.E., et al., *A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial.* Clin Vaccine Immunol, 2006. **13**(11): p. 1267-77.
48. Prud'homme, G.J., et al., *Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.* Curr Gene Ther, 2006. **6**(2): p. 243-73.
49. Hirao, L.A., et al., *Combined effects of IL-12 and electroporation enhances the potency of DNA vaccination in macaques.* Vaccine, 2008. **26**(25): p. 3112-20.
50. Rosati, M., et al., *Increased immune responses in rhesus macaques by DNA vaccination combined with electroporation.* Vaccine, 2008. **26**(40): p. 5223-9.
51. Curcio, C., et al., *DNA immunization using constant-current electroporation affords long-term protection from autochthonous mammary carcinomas in cancer-prone transgenic mice.* Cancer Gene Ther., 2008. **15**(2): p. 108-114.
52. Ugen, K.E., et al., *Regression of subcutaneous B16 melanoma tumors after intratumoral delivery of an IL-15-expressing plasmid followed by in vivo electroporation.* Cancer Gene Ther., 2006. **13**(10): p. 969-974.
53. Tebas, P., et al., *Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report.* N Engl J Med, 2017.
54. Tebas, P., et al., *Intradermal SynCon(R) Ebola GP DNA Vaccine is Temperature Stable and Safely Demonstrates Cellular and Humoral Immunogenicity Advantages in Healthy Volunteers.* J Infect Dis, 2019.
55. De Rosa, S.C., et al., *Robust antibody and cellular responses induced by DNA-only vaccination for HIV.* JCI Insight, 2020. **5**(13).
56. Chandrashekar, A., et al., *SARS-CoV-2 infection protects against rechallenge in rhesus macaques.* Science, 2020.
57. Patel, A., et al., *Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model.* bioRxiv, 2020: p. 2020.07.28.225649.
58. Andrade, V.M., et al., *INO-4800 DNA Vaccine Induces Neutralizing Antibodies and T cell Activity Against Global SARS-CoV-2 Variants.* bioRxiv, 2021: p. 2021.04.14.439719.
59. Gary E., W.B.M., Parzych E.M., Griffin B.D., Zhu X., Tailor N., Tursi N.J., Chan M., Purwar M., Vendramelli R., Choi J., Frost K.L, Reeder S., Liaw K., Tello E., Ali A.R., Yun K., Pei Y.,Thomas S.,Rghei A.D., Guilleman M.M., Muthumani K., Smith T., Wootton S.K., Patel A., Weiner D.B., Kobasa D., *A novel mouse AAV6 hACE2 transduction model of wild-type SARS-CoV-2 infection studied using synDNA immunogens.* iScience, 2021.
60. Gooch, K., et al., *One or two dose regimen of the SARS-CoV-2 synthetic DNA vaccine INO-4800 protects against respiratory tract disease burden in nonhuman primate challenge model.* Research Square 2021.
61. Trevor, S. *Development of INO-4800, a DNA-vaccine for COVID-19*. in *Keystone Symposia Antibodies and Vaccines as Drugs for COVID-19*. 2021.
62. European Commission, *Directorate-General: A Guideline on Summary of Product Characteristics (SmPC)*. 2009, EMA.

63. Diehl, M.C., et al., *Tolerability of intramuscular and intradermal delivery by CELLECTRA((R)) adaptive constant current electroporation device in healthy volunteers.* Hum Vaccin Immunother, 2013. **9**(10): p. 2246-52.

17.0 APPENDICES

17.1 APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

For the purpose of standardization across multiple vaccine platforms, including those substantially different from Inovio's platform, the below table lists AEs of special interest (AESIs) relevant to COVID-19 vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/Pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalitis/Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
	Bell's Palsy
	Transverse myelitis
	Narcolepsy
Hematologic	Thrombocytopenia
	Immune thrombocytopenia (ITP)
	Disseminated intravascular coagulation (DIC)
	Hemorrhagic stroke
	Non-hemorrhagic stroke
	Deep Vein Thrombosis (DVT)
	Pulmonary Embolism (PE)
Immunologic	Anaphylaxis
	Vasculitides
Cardiac	Acute cardiac failure
	Myocarditis/pericarditis
	Acute myocardial infarction
Other	Septic shock-like syndrome
	Appendicitis
	Multisystem Inflammatory Syndrome
	Acute kidney failure