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:	Statistical Analysis Plan Final Version 2.0 (Phase 2 segment): 20 January 2022 Statistical Analysis Plan Final Version 1.0 (Phase 3 segment): 29 July 2022

16.1.9 Documentation of Statistical Methods

Phase 2 SAP Version 2.0, dated 20 Jan 2022

Phase 3 SAP Version 1.0, dated 27 July 2022

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
Protocol Version, Date:	Final v2.0 USA; 08-OCT-2021
ICON GPHS ID:	5309-0001
Document Version, Date:	Final v2.0; 20-JAN-2022
Prepared by:	[redacted], Ph.D ICON GPHS [redacted]
On behalf of:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462

Signature Page

Prepared at ICON GPHS by:

[redacted], PhD, [redacted]

pp [redacted], [redacted], Biostatistics

Signature | Date

Approved at ICON GPHS by:

[redacted], PhD

[redacted] Principal Investigator

Signature | Date

Approved at SPONSOR by:

[redacted]

[redacted] Biostatistics

Signature | Date

Revision History

Version	Date	Revisions
0.1	16 November 2020	Initial draft
0.2	12 January 2021	Internal Review
0.3	15 March 2021	Sponsor request to split out Phase 2 from Phase 3 for clarity
1.0	9 April 2021	Final v1.0
1.1	06-DEC-2021	Revised draft to incorporate changes in protocol USA v2.0
1.2	05-JAN-2022	Revised draft to incorporate comments from Inovio: unblinding at Week 30
2.0	20-JAN-2022	Final v2.0

Table of Contents

List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
BUN	blood urea nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID19	Corona Virus Disease
CPT	cell preparation tubes
CRF	Case Report Form
CSR	Clinical Study Report
DSMB	Data Safety and Monitoring Board
ECG	electrocardiogram
ELISpot	enzyme-linked immune absorbent spot
EOS	End of Study
EP	electroporation
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
H0	null hypothesis
H1	alternative hypothesis
HCO3	bicarbonate
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent-to-treat
K	Potassium
LDH	Lactate Dehydrogenase
MAAE	Medically Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger Ribonucleic Acid
O2	Oxygen
PCR	Polymerase chain reaction
PO4	Phosphate
PP	Per Protocol
PT	Preferred Term
RT	reverse transcriptase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	standard deviation
SI	International system of units
SOC	system organ class
TEAE	Treatment Emergent Adverse Event
TLF	Table Listing and Figure
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for the study protocol COVID 19-311 version 2.0 USA "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" dated 08-OCT-2021 for the analysis of the Phase 2 portion of the trial. A subsequent SAP will be developed specific for the Phase 3 portion of the trial. The table of contents and templates for the Tables, Listings, and Figures (TLFs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 and Good Clinical Practice (GCP) guidelines.

All data analyses and generation of TLFs will be performed using SAS 9.4® or higher.

2 Study Objectives

2.1 Primary objective

- Evaluate the cellular and humoral immune response to INO-4800 administered by ID injection followed immediately by EP.

2.2 Secondary objectives

- Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP

2.3 Exploratory objective

- Evaluate the expanded immunological profile of antibody response and T cell immune response

2.4 Safety objective(s)

The safety objectives are included within the secondary objectives and include the following:

- Evaluate the safety and tolerability of INO-4800 administered by ID injection followed immediately by EP

2.5 General study design

This is an operationally seamless Phase 2/3, randomized, placebo-controlled, multicenter 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.

In the Phase 2 segment, approximately 400 subjects 18 years of age and older will be randomized at a 3:3:1:1 ratio across four dose groups (Table 1).

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 immunogenicity and safety will be produced once the Week 6 immunogenicity data and Week 8 phone call visit data are completed for all subjects in the Phase 2 segment.

The total study duration is 393 days from Screening to end of study.

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.

2.6 Randomization and blinding

At each clinical site, subjects who are eligible to enter phase 2 segment will be randomized to one of four treatment arms (INO-4800 1.0 mg, one injection; INO-4800 2.0 mg, two injections; Placebo, one injection; Placebo, two injections) in a 3:3:1:1 ratio, respectively, via the Y'Prime interactive response technology (IRT) randomization system. Randomization in this study will follow a permuted block randomization method. No stratification will be conducted.

This segment of the trial is double-blinded within dose-level, and group level unblinded summaries and analyses of immunogenicity and safety will be produced once the Week 6 immunogenicity data and Week 8 phone call visit data are completed for all subjects in the Phase 2 segment, which will be presented to the sponsor for dose selection for the Phase 3 portion. Per study protocol USA v2.0, all subjects will be unblinded when all subjects have completed the Week 30 study visit after identification and approval of the study populations.

Emergency unblinding procedures during the trial may be taken if the knowledge of the product administered is essential for the medical management of the subject by the principal investigator. Unblinding will be conducted through the IRT system. Notification to sponsor and medical monitor will be made for each unblinding and a record will be kept at each study site for all unbroken treatment codes and the reason for the need to break the treatment assignment.

2.7 Study treatments and assessments

The maximum duration of study participation from initial dosing to end of follow-up period is 393 days. The screening period can precede this active participation period by 1 to 30 days, for a total maximum duration of up to 423 days.

The investigational products (IPs) are: INO-4800, formulated in sodium chloride and sodium citrate buffer, refrigerated, and Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

Dosing regimens in 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)

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 in the protocol.

The sponsor will continuously monitor emerging results from ongoing trials. Any evidence will be assessed by the Data and Safety Monitoring Board (DSMB) who 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.

The detailed descriptions of procedures and assessments to be conducted during the Phase 2 segment in this trial are summarized in Phase 2 Segment Schedule of Events in Table 2 below.

Table 2: Phase 2 Segment Schedule of Events

Tests and assessments	Sc	D0		Tel #1	Wk 4		Tel #2	Wk6	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.
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. 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.

3 Study Endpoints

3.1 Primary endpoints

- Antigen-specific cellular immune response measured by IFN-gamma ELISpot
- Neutralizing antibody response measured by a pseudovirus-based neutralization assay

3.2 Secondary endpoints

- Incidence of solicited and unsolicited injection site reactions
- Incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity and relationship to investigational product
- Incidence of serious adverse events (SAEs)
- Incidence of adverse events of special interest (AESIs)

3.3 Exploratory endpoints

- Antigen-specific cellular immune response measured by flow cytometry.
- 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

4 Sample Size and Power

The phase 2 segment of this trial was not powered to conduct any formal hypothesis testing.

5 Analysis Populations

5.1 Analysis Population

5.1.1 Intention-To-Treat population (ITT)

The ITT population includes all subjects who are randomized. Subjects in this sample will be grouped to treatment arms as randomized.

5.1.2 Modified Intention-To-Treat population (mITT)

The 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.

5.1.3 Safety population (Safety)

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

treatment and one dose of another treatment accidently, the subject will be analyzed according to the treatments received.

5.1.4 Per-Protocol population (PP)

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 immunogenicity in the Phase 2 segment of this trial.

5.2 Protocol deviations/violations and exclusions from analysis sets

Protocol deviation data will be captured in the clinical trial management system. Extracts of all protocol deviations will be reviewed periodically and prior to final analysis. All protocol deviations and the exclusion of participants from analysis sets will be identified prior to unblinding, through clinical review input provided by the sponsor, using the following sources of information:

- Supportive participant listings, provided by the ICON statistician based upon data recorded in the clinical trial management system

Further, deviations from the protocol will be classified as major or minor. Classification of major and minor protocol deviations is determined prior to participant enrollment and is outlined in detail in the protocol deviation criteria documentation managed by the clinical trial management team.

6 Statistical Considerations and Analysis

6.1 Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, baseline derivation and other important derivations applicable for this segment of the trial.

Table 3: Derived Variables

Demographic and Baseline Characteristics	
Body Mass Index	Weight (kg) / [height (m)] ^2
Age	Calculated at the time of informed consent. Sample SAS code to calculate age is: age = floor ((intck('month', date of birth, informed consent date) – (day(informed consent date) < day(date of birth))) / 12)

Baseline	Baseline is defined as the last measurement prior to the first treatment administration
Derivation of Durations	
Study day at any visit	Date of interest – date of first dose. One day is added if the difference is ≥ 0.
Duration of any events	End Date of Event – Start date of event + 1
Other Derivations	
Incidence in a group	The proportion of the participants experiencing the outcome of interest compared to the total number of participants at risk of experiencing the outcome of interest. (e.g. the incident rate of SAEs after vaccination are the number of participants with an SAE reported after vaccination divided by the number of participants that received the vaccination).
Geometric Mean Fold Rise (GMFR)	The ratio of the geometric mean post-baseline result to the geometric mean baseline result of a particular lab/assay result.

6.2 Handling of missing data and outliers

6.2.1 Missing data analysis methods

No imputations will be conducted for missing data.

6.2.1.1 Handling of missing or incomplete dates

Imputation rules for missing or partial adverse event start/stop dates

- If the AE start date day is missing (month and year provided) then set the date to the first of the month, unless the month and year are the same as the first dose. In this case, set the date to the date of first dose.
- If the AE start month is missing (day and year provided) then set the month to January, unless the day and year are the same as the year of the first dose. In this case, set the date to the date of first dose.
- If the AE start date day and month are missing (year is provided) then set the month and day to January 1, unless the year is the same as the year of the first dose. In this case, set the date to the date of first dose.
- If the AE end date day is missing (month and year provided) then set the date to the last day of the month.

- If the AE end date month is missing (day and year provided) then set the date to the latest calendar month consistent with the day.
- If the AE end date day and month is missing (year is provided) then set the date to December 31.
- If the year of the AE start date or AE end date are missing, then a query to the site must be made to gather additional information.
    - If the start date is completely missing, then set the start date to the date of first dose. If the end date is completely missing, then set the end date to the date of latest follow-up.
    - If the start date day is missing (month provided), then set the date to the first of the month, unless the month is the same as the first dose. In this case, set the date to the date of first dose. If the end date day is missing (month provided), then set the date to the last day of the month.
    - If the start date month is missing (day provided), then set the month date to January, unless the day is the same as the first dose. In this case, set the date to the date of first dose. If the end date month is missing (day provided), then set the date to the latest calendar month consistent with the day.
    - If the start date year is missing (day and month provided), then set the year to the year in which the patient was first screened, unless the day and month are the same as the first dose. In this case, set the date to the date of first dose. If the end date year is missing (day and month provided), then set the date to the latest calendar year in which the patient is followed.

Imputation rules for missing or partial prior/concomitant medication start/stop dates

- Start dates will not be imputed.
- Partial stop dates of prior/concomitant medications will be assumed to be the latest possible date consistent with the partial date. If day, month, and year are missing assign ‘continuing’ status to the stop date.

7 Statistical Methods

7.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum. Means and medians will be rounded to one more

decimal place than what is reported in the data. Standard deviations will be rounded to two more decimal places than what is reported in the data.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline is defined as the last measurement prior to the first treatment administration. All summaries will be presented by treatment group, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings. All listings will be sorted by investigational site, subject ID, date/time and visit. The treatment group as well as the patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized (ITT Population).

7.2 Subject disposition

Subject disposition information will be summarized by treatment group, age stratum, race, ethnicity, sex at birth, country, and overall. A CONSORT diagram will be constructed that details the number of subjects screened, the number enrolled and eligible for vaccination, the number randomized to each trial arm, the number receiving the first and second vaccination, the number of early terminations, the number completing the study, and the number eligible for analysis.

The primary reason for early withdrawal will also be tabulated.

The number of subjects randomized will be used as the denominator for the proportion calculation. Subject disposition will be listed along with inclusion or exclusion criteria that were not met for randomization.

The number and percent of subjects in each analysis set will also be tabulated. A listing of each subject excluded from an analysis population will be listed as well as the reason why they were excluded from the population.

Treatment misallocations occur when a subject received a different treatment than they were randomized to. In these cases:

- If a subject was randomized but not treated, then the subject will be included with their randomized treatment group the subject disposition summaries. These subjects will be included in the ITT population only.
- If a subject was treated but not randomized, then by definition the subject will be excluded from the immunogenicity analyses since randomized treatment is missing but will be included in the ITT population and in the Safety population according to the treatment actually received for all safety analyses.

- If a subject was randomized but received a different treatment regimen, then the subject will be included according to their randomized treatment group for all immunogenicity analyses in the ITT/mITT population but will be excluded from immunogenicity analyses in the PP population. These subjects will be included according to the treatment regimen actually received for all safety analyses.

7.3 Protocol deviations/violations

The number of patients excluded from ITT, mITT, Safety, and Per-protocol analysis sets and reasons for exclusion will be summarized by treatment group and overall. Population membership details will be listed, including reason for exclusion from each population (on randomized subjects).

Protocol deviations will also be listed.

7.4 Demographics and baseline characteristics

7.4.1 Demographics

Age at consent, height, weight, and other continuous demographic variables at baseline will be summarized descriptively. Sex, primary race, ethnicity, and other categorical variables will be summarized using the ITT and PP populations.

7.4.2 Medical history

Medical history will be listed.

7.4.3 Prior and concomitant medications

Data for all prior and concomitant medications will be summarized with percentages by treatment arm, for the ITT and PP populations.

Prior and concomitant medications will also be listed.

7.5 Extent of exposure

7.5.1 Treatment duration

Study treatment exposure will be summarized as the number of subjects receiving a total of 1 and 2 doses of product and will be presented by treatment group on the ITT, mITT, PP, and safety populations.

7.5.2 Treatment compliance

A full course of study product administration consists of two doses of vaccine. A summary table detailing the total number of doses received will be presented along with the reason a dose was not administered or missed. A summary of subjects receiving the dose outside the dosing window, 25 to 31 days post first dose, will be presented.

7.6 Immunogenicity analysis

The immunogenicity analyses will be performed using the PP population. Valid samples for statistical analysis purposes will include 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 analyses will be stratified according to NP positive/negative status of the subjects, prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects, and age group. Strata for age group are 18 – 50, 51+ and 65+ years at Dose 1. Strata for NP status are positive and negative at each time point (week 6, week 30, and week 56). Strata for prior receipt of any non-study prophylactic COVID-19 vaccine are yes and no at each time point. Additionally, a composite stratification of NP positive or non-study vaccinated and NP negative and not non-study vaccinated will be utilized.

At each post baseline time point, post-baseline increase from baseline in interferon-γ ELISpot magnitude and post baseline increase from baseline in cellular immune magnitude measured by flow cytometry will be summarized using the median by treatment group. Differences in medians and associated nonparametric 95% CIs between treatment groups will be calculated.

The following sample of SAS code will be used to construct these confidence intervals.

```
proc npar1way hl alpha=.05 data=<DATASET>;
   class armcd;
   var <OUTCOME>;
   exact hl;
   ods select HodgesLehmann;
run;
```

In above SAS codes:

- Armcd represents active treatment and placebo, i.e., 1.0 mg INO-4800, 1injection placebo, or 2.0 mg INO-4800, and 2 injections placebo.
- OUTCOME represents interferon-γ ELISpot or flow cytometry increases from baseline.
- hl adds Hodges-Lehmann confidence interval for location differences between treatment groups.

At each post baseline time point, post-baseline changes in neutralizing antibody (PRNT50) titers from ELISA will be summarized with GMFRs by treatment group. The GMFRs will be compared between treatment groups using ratios and associated 95% t-distribution based CIs.

The following sample of SAS code will be used to construct these confidence intervals.

```
proc mixed data=<DATASET>;
   class armcd(ref='xx');
   model LR = armcd;
   lsmeans armcd / cl diff alpha=0.05;
   ods output diffs=diff;
run;
```

```
data diff1; set diff;
   GMFR=10**(Estimate);
   Lclm=10**(lower);
   Uclm=10**(upper);
run;
```

In above SAS codes:

- Armcd represents active treatment and placebo, i.e., 1.0 mg INO-4800, 1 injection placebo, or 2.0 mg INO-4800, and 2 injections placebo.
- LR represents $\log_{10}$ Yi/ Bi, where Yi is the post dose assay result for subject i; and Bi is the baseline assay result for subject i.
- xx represents reference arm (i.e., 1 injection placebo or 2 injection placebo or 1.0 mg INO-4800 or 2.0 mg INO-4800)

7.7 Safety analysis

This section describes the safety analyses that will be conducted including all data collected in subjects who drop out.

All definitions relative to safety endpoints are detailed in Section 3.

Safety analyses will be conducted on the safety population and will be performed for all safety variables specified below. All safety data will be summarized by treatment group. The summaries/analyses will be stratified according to NP positive/negative status of the subjects, prior receipt of any non-study prophylactic COVID-19 vaccine of the subjects, and age group. Strata for age group are 18 – 50, 51+ and 65+ years at Dose 1. Strata for NP status are positive and negative at each time point. Strata for prior receipt of any non-study prophylactic COVID-19 vaccine are yes and no at each time point. Additionally, a composite stratification of NP positive or non-study vaccinated and NP negative and not non-study vaccinated will be utilized.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, ECG) will include subjects from the safety population who have data available for both the baseline and the time point under considerations unless otherwise specified.

7.7.1 Adverse events

All adverse events (AE) will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

In summaries by SOC and PT, adverse events will be sorted by descending frequency within each SOC and PT according to the total number of events. In summaries by PT, AEs will be sorted by decreasing frequency according to the total number of events.

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.

AEs will be classified as pre-treatment or treatment emergent (TEAE) defined as follows:

- Pre-treatment: any AE that started before the first dose date of the study treatment
- TEAE: any AE that was newly developed at or after the first dose date of study treatment

Details for imputing missing or partial start dates of adverse events are described in section 6.2.

AE summary tables will include the following:

- All TEAEs
- Related TEAEs (AE will be defined as related if causality is either probable, possible, or definite)
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

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.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in the treatment period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in the treatment period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

Adverse events by severity and separately by relationship will be summarized based on the most intense event during the treatment period and strongest relationship to study treatment, respectively.

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 following sample of SAS code will be used to construct confidence intervals of the risk difference with the method of Miettinen and Nurminen:

```
proc freq data = <DATASET>;
  tables armcd * <OUTCOME> / riskdiff(CL= MN);
```

```
  weight <COUNT>;
run;
```

7.7.2 Clinical laboratory evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in the International System of Units (SI). If a lab value is reported using a nonnumeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

All laboratory data obtained after the start of study medication dosing up to and including the final visit will be used for the laboratory safety analysis. Laboratory summaries will be provided including values measured during the follow-up period, where appropriate.

Visit value and change and/or percent change from baseline (where applicable) will be summarized by treatment group using descriptive statistics for all laboratory parameters which are listed in the protocol.

Shift tables among the safety population will be summarized by treatment group using the baseline values and highest/lowest values obtained post baseline. Lab results will be classified as Normal or Abnormal based upon local laboratory normal ranges.

7.7.3 Vital signs

Visit values and changes from baseline for vital sign measurements (pulse, blood pressure, SpO2, temperature, respiratory rate) will be summarized by treatment group at each visit using descriptive statistics. Visit values will be calculated as the mean of all available measurements per parameter.

7.8 Interim analysis

For safety issues or evidence of poor efficacy, the DSMB could recommend stopping enrollment at any time; no formal interim analysis for this segment of the trial will be performed.

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.

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, once all subjects have reached the Week 30 Visit timepoint, all subjects will be unblinded (as specified in study protocol USA v2.0).

8 Changes to Planned Analysis from Study Protocol

Not applicable.

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
Protocol Version, Date:	Version 6.0, 30 April 2021
ICON GPHS ID:	0131-0017
Document Version, Date:	Final version 1.0; 27 July 2022
Prepared by:	[redacted] PhD CStat. ICON GPHS
On behalf of:	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462

Signature Page

Prepared at ICON GPHS by:

[redacted], PhD CStat.
[redacted] Biostatistics

[redacted] 29 Jul 2022 06:17:09 (-07:00)

REASON: I am the author of this document.

53c3504f-87ed-417e-8163-70802f734a34

Signature Date

Reviewed at ICON GPHS by:

[redacted], PhD
[redacted]Principal Investigator

[redacted] 29 Jul 2022 09:51:53 (-07:00)

REASON: I am approving this document.

9816d509-bba8-4dcc-969a-b838369ce510

Signature Date

Approved at Inovio Pharmaceuticals, Inc. by:

[redacted], PhD
[redacted]Biostatistics

Signature Date

Revision History

Version	Date	Revisions
0.1	29-September-2021	Initial draft
0.2	29-September-2021	Revised draft after internal review.
0.3	17-November-2021	Revised draft addressing comments from sponsor.
0.4	22-June-22	The study has been terminated, analysis will be restricted to primary efficacy and safety.
0.5	04-July-2022	Revised following sponsor comments.
1.0	27-Jul-22	Update schedule of assessments from protocol version 6 and removed lab analyses Final version

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

List of Abbreviations

Abbreviation	Explanation
AE	adverse event
AESIs	adverse events of special interest
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
CI	Confidence Interval
COVID-19	coronavirus disease 2019
CPT	Cell Preparation Tubes
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography (scan)
CYP3A	cytochrome P450 3A4
DRC	Democratic Republic of the Congo
DSMB	Data and Safety Monitoring Board
EAC	Endpoint Adjudication Committee
EC	Ethic Committee
ECG	electrocardiogram
EOS	end of study
EP	electroporation
FACTS	fixed and adaptive clinical trial simulator
GCP	Good Clinical Practice
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	intradermal
IP	investigational product
IRT	Interactive Response Technology
ITT	intention-to-treat (population)
mITT	modified intention-to-treat (population)
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council
PAR	paracetamol
PP	per protocol
PT	Preferred Term
QTc	corrected QT interval
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acquired respiratory syndrome - coronavirus 2
SD	standard deviation
SI	International System of Units
SOC	system-organ class
SpO2	blood oxygen saturation level
SSC	saline sodium citrate
SSG	Statistical Support Group
TBD	to be determined
TEAE	treatment emergent adverse event
TLF(s)	Table(s), Listing(s), and Figure(s)
WHO	World Health Organization

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for study protocol COVID19-311 version 6.0 "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" dated 30 April 2021 for the analysis of the Phase 3 segment of the trial. The table of contents and templates for the Tables, Listings, and Figures (TLFs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Council for Harmonization (ICH) E9 and Good Clinical Practice (GCP) guidelines.

1.1 Study Objectives

The overall purpose of this clinical trial is to evaluate the safety, immunogenicity, and efficacy of INO-4800 to prevent COVID-19 in subjects at high risk of exposure to SARS-CoV-2.

1.1.1 Primary objective

The primary objective of this clinical trial is to evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline.

1.1.2 Secondary objectives

The secondary objectives of this clinical trial are:

1. To evaluate the safety and tolerability of INO-4800.
2. To 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.
3. To evaluate the cellular and humoral immune response to INO-4800.
4. To evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 seropositive at baseline.

1.1.3 Exploratory objectives

The exploratory objectives of this clinical trial are:

1. To 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.
2. To 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.

3. To evaluate the immunological profile by assessing both antibody response and T cell immune response.

4. To evaluate antibody persistence.

1.2 Study Design

1.2.1 Design Configuration

This SAP pertains to the Phase 3 segment of an operationally seamless Phase 2/3, randomized, placebo-controlled, multi-center trial to evaluate the efficacy, safety, and immunogenicity 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. The subjects and data from Phase 3 are independent from that of Phase 2. 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). 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.

The Phase 3 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 study's primary efficacy 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. All 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).

The total study duration is 393 days from screening to study discharge/EOS.

The Data Safety Monitoring Board (DSMB) will convene regularly to review all available unblinded efficacy and safety data. Additionally, an independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases.

1.2.2 Randomization and Blinding

This study is double blinded. 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 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.

Randomization in this trial will be conducted by YPrime. 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, 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/mm^3 or undetectable viral load)
- Liver disease
- Obesity (BMI ≥ 30 kg/m^2)
- Sickle cell disease or thalassemia, or
- Smoking (current or former smoker).

Table 1: Sample Size for Randomization

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 Phase 3 segment of the clinical 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.

Study staff at each site (coordinators and PI) along with the participants, and sponsor representatives will be blinded throughout the course of the trial. At ICON, unblinded personnel will consist of a biostatistician and statistical programmer. The DSMB members will also be unblinded. Emergency unblinding procedures may be taken if the knowledge of the product administered is essential for the medical management of the participant by the principal investigator. Individual, emergency participant unblinding will be conducted through the IRT system. Notification to sponsor and medical monitor and associated documentation will be made for each unblinding.

Formal unblinding of the trial will be done after database lock and after identification and approval of the per-protocol analysis set.

1.2.3 Study Duration

The maximum duration for study participation from screening to end of follow-up period is 393 days.

1.2.4 Study Treatments and Assessments

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

Dosing regimens in Phase 3 Segment:

- Active Investigational Product: Two 1.0 mg 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).

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 in the Protocol 6.1.2.

The Data and Safety Monitoring Board (DSMB) will advise regarding any safety concerns and will make recommendations regarding continued enrollment, safety pause, and trial suspension. If the safety data are considered unfavorable during any safety review, the DSMB may recommend a trial pause or trial termination. The Sponsor will perform an investigation and consult with the DSMB and other experts, if

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

needed, to determine whether to resume dosing of the remainder of the subjects. For further details, see the DSMB Charter.

The detailed descriptions of procedures and assessments to be conducted during this study are summarized in the Phase 3 Schedule of Events in Appendix A.

1.2.5 Sample Size and Power

The Phase 3 segment of this 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%, with a one-sided type 1 error of 0.022. A sample size of 6714 baseline SARS-CoV-2 seronegative subjects will be required to achieve 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.

2. Types of Planned Analyses

2.1 Data Safety Monitoring Board Analyses

The DSMB will meet approximately monthly until all subjects are enrolled in the trial, then bimonthly once all subjects are enrolled for the duration of the trial. The DSMB may also meet ad hoc as needed outside of the scheduled meetings and shall be disbanded upon completion of the trial.

The following data/documents will be generated for DSMB review:

- Baseline characteristics, demographics, participant disposition.
- Adverse events (AEs), adverse event of special interest (AESI), medically attended adverse events (MAAEs), and serious adverse events (SAEs).
    - Tabulated for each trial group by system organ class (SOC) and preferred term (PT), severity, seriousness, duration, treatment given, and the relationship to the trial drug and device.
    - Clinical test results and laboratory values (including raw values, changes from baseline, and clinical abnormalities).
- Listing of administration (injection) site reactions, including grading, duration, and treatment provided.
- Listing of deaths.
- COVID-19 disease.
- Any other supporting data requested by the DSMB.

2.2 Interim Analyses

Two formal interim analyses of efficacy are planned for review by the independent DSMB, as described in the clinical protocol and in the DSMB Charter: one at 50% (75 cases) and one at 75% (112 cases) of the total required cases for the primary endpoint (149 cases). However, the trial has been terminated prior to

observing 75 cases, and therefore, these analyses will not be conducted. For safety issues, the DSMB could recommend stopping enrollment at any time; no formal interim analysis will be performed for this purpose.

Therefore, the two-sided type I error of 0.05 will not be adjusted for interim analyses.

3. General Considerations for Data Analysis

3.1 Analysis Populations

3.1.1 Intention-To-Treat population (ITT)

The ITT population includes all subjects who are randomized, regardless of protocol violations or missing data. Subjects in this sample will be grouped to treatment arms as randomized. Analysis of the ITT population will be considered supportive for the corresponding Per-Protocol population for the analysis of efficacy.

3.1.2 Modified Intention-To-Treat population (mITT)

The 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 Per-Protocol population for the analysis of efficacy.

3.1.3 Safety population (Safety)

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.

3.1.4 Per-Protocol population (PP)

The 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 of the PP population among those who are baseline SARS-CoV-2 seronegative will be primary for the analysis of efficacy.

3.2 Strata and Covariates

SARS-CoV-2 serostatus at baseline will be used as a stratification factor for several analyses. No covariates will be included in the analyses.

3.3 Multiplicity

Not applicable.

3.4 Derived Variables

Derived variables for demographic and baseline characteristics, various duration derivations, and other derivations are listed in Table 2.

Table 2: Derived Variables

Variables	Formula
Demographic and Baseline Characteristics	
Body Mass Index	Weight (kg) / [height (m)] ^2
Derivation of Durations	
Study day at any visit	Date of interest – date of first dose of trial vaccine. One day is added if the difference is ≥ 0.
Duration of any events	End Date of Event – Start date of event + 1
Baseline Derivations	
Baseline	The baseline value is defined as the last observation prior to or on the date of the first dose of study drug; missing data will not be imputed.
Change from baseline	Post baseline value – Baseline; missing data will not be imputed.
Other Derivations	
Incidence	The number of subjects with a specific event divided by the total follow up time (in days) among the subjects in the treatment or control group and at risk of an initial occurrence of the event.
p	The true proportion of subjects with disease who receive INO-4800 relative to the total number of subjects with disease.
k	The total amount of follow-up time (in days) in the placebo group divided by the total amount of follow-up time (in days) in the INO-4800 group 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). The primary hypothesis of relative efficacy greater than 30% will be tested with H_0: p ≥ .70/(.70+k) vs. H_1: p < .70/(.70+k).
Vaccine Efficacy	1 – Risk in the vaccinated group / Risk in the unvaccinated group* 100, where risk is defined as the number of subjects with disease divided by the number of subjects in risk. Also equal to (1-(1+k)p)/(1-p), where k and p are defined above.
Confidence interval for efficacy	[(1-(1+k)UBp)/(1-UBp), (1-(1+k)LBp)/(1-LBp)],where UB and LB are the Clopper-Pearson upper and lower limits for the proportion, p; and p and k are defined above.
Geometric mean titer (GMT)	GMT is calculated as anti-$\log_{10}$ (mean [$\log_{10}$ Ti]) where Ti is the assay result for subject i.
Geometric mean fold rise (GMFR)	GMFR is calculated as anti-$\log_{10}$ (mean [$\log_{10}$ (Yi/ Bi)]) where Yi is the post dose assay result for subject i; and Bi is the baseline assay result for subject i.

3.5 Handling of Missing Data and Outliers

No imputations will be conducted for missing data. No data will be excluded for being an outlier.

3.5.1 Missing data analysis methods

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

3.5.2 Missing or incomplete dates

3.5.2.1 Imputation rules for missing or partial AE start/stop dates

- If the AE start date day is missing (month and year provided) then set the date to the first of the month, unless the month and year are the same as the first dose. In this case, set the date to the date of first dose.
- If the AE start month is missing (day and year provided) then set the month to January, unless the day and year are the same as the year of the first dose. In this case, set the date to the date of first dose.
- If the AE start date day and month are missing (year is provided) then set the month and day to January 1, unless the year is the same as the year of the first dose. In this case, set the date to the date of first dose.
- If the AE end date day is missing (month and year provided) then set the date to the last day of the month.
- If the AE end date month is missing (day and year provided) then set the date to the latest calendar month consistent with the day.
- If the AE end date month is missing (year is provided) then set the date to December 31.
- If the year of the AE start date or AE end date are missing, then a query to the site must be made to gather additional information.
    - If the start date is completely missing, then set the start date to the date of first dose. If the end date is completely missing, then set the end date to the date of latest follow-up.
    - If the start date day is missing (month provided), then set the date to the first of the month, unless the month is the same as the first dose. In this case, set the date to the date of first dose. If the end date day is missing (month provided), then set the date to the last day of the month.
    - If the start date month is missing (day provided), then set the month date to January, unless the day is the same as the first dose. In this case, set the date to the date of first dose. If the end date month is missing (day provided), then set the date to the latest calendar month consistent with the day.

- If the start date year is missing (day and month provided), then set the year to the year in which the patient was first screened, unless the day and month are the same as the first dose. In this case, set the date to the date of first dose. If the end date year is missing (day and month provided), then set the date to the latest calendar year in which the patient is followed.

3.5.2.2 Imputation rules for missing or partial medication start/stop dates

- Start dates will not be imputed.
- Partial stop dates will be assumed to be the latest possible date consistent with the partial date. If day, month, and year are missing assign 'continuing' status to the stop date.

3.6 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum. Means and medians will be rounded to one more decimal place than what is reported in the data. Standard deviations will be rounded to two more decimal places than what is reported in the data.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last available pre-dose value. All summaries will be presented by treatment group and SARS-CoV-2 serostatus at baseline, unless otherwise specified.

For any subject who receives an approved COVID19 vaccine after being dosed with INO-4800/placebo, the follow-up time will be divided to account for pre- and post- receipt of approved vaccine. For the main analyses and summaries of efficacy, data from the pre- receipt of an approved vaccine period will be used.

Subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by treatment, subject ID, date/time, and visit. The treatment group, as well as the patient's sex and age, will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized (ITT population).

3.7 Disposition of Subjects

Subject disposition will be summarized by treatment arm and overall, as well as SARS-CoV-2 serostatus at baseline. The number and percent of subjects screened, screened failure, randomized to each trial arm, receiving the first and second dose, early terminations, and completing the study will be summarized. The

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

number of subjects randomized will be used as the denominator for the proportion calculation. The number in each analysis population will also be tabulated. Subject disposition will be listed along with inclusion or exclusion criteria that were not met for randomization, and the primary reason for early withdrawal will also be tabulated. Subject enrollment by site will also be tabulated by treatment arm and overall.

Treatment misallocations occur when a subject received a different treatment than they were randomized. In these cases:

- If a subject was randomized but not treated, then they will be reported under their randomized treatment group in the subject disposition summaries. These subjects will be included in the ITT population only.
- If a subject was treated but not randomized, then by definition they will be excluded from the efficacy analyses because randomized treatment is missing but will be included in the ITT population and in the Safety population according to the treatment actually received for all safety analyses.
- If a subject was randomized but received a different treatment, then the subject will be included according to their randomized treatment group for all efficacy analyses in the ITT/mITT population but will be excluded from the efficacy analyses in the PP population. These subjects will be included according to treatment they actually received for all safety analyses.

3.8 Extent of Exposure and Compliance

3.8.1 Treatment Duration

Study treatment exposure will be summarized as the number of subjects receiving a total of 1 or 2 doses of product and will be presented by treatment group, as well as SARS-CoV-2 serostatus at baseline on the ITT mITT, PP, and safety populations.

3.8.2 Treatment Compliance

A full course of study product administration consists of 2 doses of vaccine. A summary by treatment group, as well as SARS-CoV-2 serostatus at baseline detailing the total number of doses received will be presented along with the reason a second dose was not administered or missed. A summary of subjects receiving the second dose outside the dosing window, 25 to 31 days post first dose, will be presented.

3.9 Protocol Deviations/violations and exclusions from analysis sets

Protocol deviation data will be captured in the clinical trial management system. Extracts of all protocol deviations will be reviewed periodically and prior to interim and final analyses. All protocol deviations and the exclusion of participants from analysis sets will be identified prior to unblinding through clinical review input provided by the sponsor using supportive participant listings provided by the ICON GPHS statistician based upon data recorded in the clinical trial management system.

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

Further, deviations from the protocol will be classified as major or minor. Classification of major and minor protocol deviations is determined prior to participant enrollment and is outlined in detail in the protocol deviation criteria documentation managed by the clinical trial management team. A summary table presenting protocol deviations will be generated by treatment arm and SARS-CoV-2 serostatus at baseline for the ITT population. Protocol deviations will also be listed.

The number of subjects excluded from mITT, Safety, and Per-Protocol analysis sets and reasons for exclusions will be summarized by treatment group and overall, as well as SARS-CoV-2 serostatus at baseline.

Population membership details will be listed, including reason for exclusion from each population (on randomized subjects).

4. Baseline Characteristics and Demographics

4.1 Baseline Characteristics

Age group (18-50, ≥ 51 years), baseline SARS-CoV-2 serostatus, and the presence of any increased risk factor (listed in SAP section 1.2.2) in subjects will be summarized using frequency counts and proportions for qualitative results for the ITT and PP populations.

4.2 Medical History

A summary of prior and concomitant medical conditions and surgical procedures will be presented by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Affairs (MedDRA) version 23.0, by treatment arm and SARS-CoV-2 serostatus at baseline.

4.3 Demographics

Demographic data will be summarized with descriptive statistics, including mean, standard deviation, minimum, median, and maximum values for continuous variables and frequency counts and percentages for categorical variables, by treatment arm and SARS-CoV-2 serostatus at baseline.

Age, height, weight, body mass index (BMI) and other continuous demographic variables at baseline will be summarized descriptively. Sex, primary race, ethnicity, and other categorical variables will be summarized using the ITT and PP populations.

4.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHODrug version Mar2020 B3).

Prohibited prior and concomitant medications are described in the protocol. This list includes medications for the prevention of COVID-19 and influenza vaccinations received within 2 weeks prior to the first dose of IP, or within 2 weeks of (before or after) any subsequent dose of IP.

4.4.1.1 Prior Medications

Prior medications are those that were stopped before the start of the trial. Data for all prior medications will be summarized descriptively by ATC class and preferred name using percentages by treatment arm and SARS-CoV-2 serostatus at baseline, for the ITT and PP populations.

4.4.1.2 Concomitant Medications

Concomitant medications include all medications, including vaccines, used by subjects during the course of the trial stopped on or after the start of the trial. Data for all concomitant medications will be summarized descriptively by ATC class and preferred name using percentages by treatment arm and SARS-CoV-2 serostatus at baseline, for the ITT and PP populations.

5. Efficacy, Immunogenicity, and Safety Analyses

5.1 Primary Analysis

The primary objective of this clinical trial is to evaluate the efficacy of INO-4800 in the prevention of COVID-19 disease in subjects who are SARS-CoV-2 negative at baseline.

5.1.1 Primary Endpoint

The primary endpoint is the first occurrence of virologically-confirmed COVID-19 disease with onset during a surveillance period from 14 days after completion of the 2-dose regimen up to 12 months post-dose 2 (EOS) in subjects who are SARS-CoV-2 seronegative at baseline.

An independent, blinded Endpoint Adjudication Committee (EAC) will review and confirm COVID-19 cases. Details of committee's scope will be provided in the respective charter.

5.1.2 Statistical Hypothesis for the Primary Efficacy Endpoint

The primary hypothesis is that INO-4800 will be efficacious relative to placebo (vaccine efficacy > 30%) among baseline SARS-CoV-2 seronegative subjects. The null hypothesis given below will be tested against the alternative hypothesis:

$$H_0: p \geq .70/(.70+k)$$

$$H_1: p < .70/(.70+k)$$

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. 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).

However, the trial has been terminated, and therefore, this hypothesis test will not be conducted. A confidence interval (detailed in the following section) will be used for analysis.

5.1.3 Analysis of Primary Efficacy

The Clopper-Pearson method will be used to compute the 95% confidence interval for the primary efficacy analysis. The outcome variable will be incidence of virologically-confirmed COVID-19 disease starting 14 days after completion of the 2-dose regimen until 12 months post-dose 2 (EOS).

This methodology is based on the assumption that the number of subjects who are cases in the INO-4800 and placebo group follows a Poisson distribution with parameter λ_v and λ_c, respectively, and 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 = $(1-(1+k)p)/(1-p)$. 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, respectively.

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 among those who are baseline SARS-CoV-2 seronegative will be primary for the analysis of efficacy in this trial.

The following sample SAS code will be used to construct the exact binomial method of Clopper-Pearson:

```
proc freq data = <DATASET>;
      tables <OUTCOME> /binomial(CL= CLOPPERPEARSON);
      exact binomial;

run;
```

5.1.4 Sensitivity Analysis

Efficacy analysis using the mITT population will also be conducted counting cases from 14 days post dose 1 as a supportive analysis. The ITT population will also be used for a supportive analysis counting cases starting from randomization.

5.1.5 Changes from Protocol-Specified Primary Efficacy Analysis

Because the trial has been terminated, neither the interim nor the final hypothesis testing will be conducted.

5.2 Secondary Efficacy and Immunogenicity Analyses

No secondary efficacy or immunogenicity endpoints will be analyzed.

5.3 Exploratory Efficacy and Immunogenicity Analyses

No exploratory efficacy or immunogenicity endpoints will be analyzed.

5.4 Safety Analysis

The safety endpoints include:

- The incidence of solicited and unsolicited injection site reactions.
- The incidence of solicited and unsolicited systemic adverse events (AEs) by system organ class (SOC), preferred term (PT), severity, and relationship to investigational product.
- The incidence of serious adverse events (SAEs).
- The incidence of adverse events of special interest (AESIs).
- The incidence of all-cause mortality.

Safety analyses will be conducted on the safety population and will be performed for all safety variables specified below. All safety data will be summarized and analyzed by treatment group and SARS-CoV-2 serostatus at baseline.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, ECG) will only include subjects from the safety population who have data available from both the baseline and the time point under consideration unless otherwise specified.

5.4.1 Adverse Events and Deaths

All AEs will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

In summaries by SOC and PT, AEs will be sorted by descending frequency within each SOC and PT according to the total number of events. In summaries by PT, AEs will be sorted by descending frequency according to the total number of events.

AEs will be classified as pre-treatment or treatment emergent (TEAE) defined as follows:

- Pre-treatment: any AE that started before the first dose date of the study treatment
- TEAE: Any AE that was newly developed at or after the first dose date of study treatment.

Details for imputing missing or partial start dates of AEs are described in SAP section 3.5.2.1.

AE summaries will include the following:

- All TEAEs
- Related TEAEs (AE will be defined as related if causality is either probably, possible, or definite)
- TEAEs by maximum severity, including grade ≥3
- Medically Attended AEs
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

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. In addition, an overall summary for categories above will be prepared by treatment arm.

Where a subject has the same AE, based on preferred terminology, reported multiple times in the treatment period, the subject will only be counted once at the preferred terminology level in AE frequency.

Where a subject has multiple AEs within the same system organ class in the treatment period, the subject will only be counted once at the system organ class level in AE frequency.

Adverse events by severity and separately by relationship will be summarized based on the most intense event during the treatment period and strongest relationship to study treatment, respectively.

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 following sample SAS code will be used to construct confidence intervals of the risk difference with the method of Miettinen and Nurminen:

```
proc freq data = <DATASET>;
      tables armcd * <OUTCOME> / riskdiff(CL=(MN));
run;
```

5.4.2 Vital signs

Measurements for vital signs (pulse, blood pressure, SpO2, temperature, respiratory rate) as well as changes from baseline will be summarized with descriptive statistics. Visit values will be calculated as the mean of all available measurements per parameter.

5.4.3 Changes from Protocol-Specified Safety Analysis

Not applicable.

DocUUID : 6875f1ec-ae51-4edd-90bb-d27ff0e18114

6. Appendices

6.1 Appendix A – Phase 3 Schedule of Events

Tests and assessments	Sc	D0		Tel #1	Wk 4		Wk6	Tel #2-6	Wk 18	Tel #7-11	Wk 30	Tel #12-13	Wk4 2	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	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.