Official Title: Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

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MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Sponsored by:
Inovio Pharmaceuticals, Inc.

Protocol Version: 1.0

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Medical Monitor Approval Page

Drug: INO-4700

Sponsor: Inovio Pharmaceuticals, Inc.
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Date (ddMmmyyyy)

CONFIDENTIAL

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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: _____

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Number: MERS-201

Clinical Trial Phase: 2a

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately nine (9) to ten (10) centers in the Middle East and Africa Regions. Additional sites and countries may be added as necessary.

Clinical Trial Design:

This is a Phase 2a, randomized, blinded, placebo-controlled, multi-center trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered by intradermal (ID) injection followed by electroporation (EP) using the CELLECTRA™ 2000 device in healthy adult volunteers. The primary objectives of this trial are to evaluate the tolerability, safety and immunogenicity of INO-4700 administered by ID injection followed by EP in healthy adult volunteers according to the regimens outlined in Table 1, Table 2, Table 3 and Figure 1.

Approximately 542 healthy volunteers will be evaluated across two (2) parts of this study, Part 1 and Part 2. INO-4700 or placebo (SSC-0001) will be administered ID in ~0.1 mL dose volume followed immediately by EP.

Part 1 – Dose Finding

In Part 1, approximately 192 participants ages 18-50 years will be assessed through five (5) dose levels and regimens. These five (5) dose levels and regimens will be evaluated across nine (9) groups designated Study Groups A, B, C, D, E, F, G, H and I. Study Groups A, B, C, D and E will receive INO-4700 and enroll approximately 32 participants per group. Study Groups F, G, H and I will receive placebo and enroll approximately 8 participants per group.

Table 1: MERS-201 Part 1 Dose Groups

	Study Group	Number of Participants	Dosing Weeks	Number of Injections + EP per Dosing Visit	INO-4700 (mg) per injection	Total Dose of INO-4700 (mg)
Active	A	32	0, 4	1	0.6	1.2
	B	32	0, 4	1	1.0	2.0
	C	32	0, 8	1	1.0	2.0
	D	32	0, 8	2[a]	0.5 + 0.5 (1.0)	2.0
	E	32	0, 4	2[a]	1.0 + 1.0 (2.0)	4.0
Total Active		**160**				
Placebo	F	8	0, 4	1	–	–
	G	8	0, 8	1	–	–
	H	8	0, 8	2[a]	–	–
	I	8	0, 4	2[a]	–	–
Total Placebo		**32**				
Total		**192**				

[a]INO-4700 will be injected ID followed by EP in an acceptable location on two different limbs at each dosing visit

Participants will be randomized to receive either INO-4700 or placebo according to the dosing schedule described in Table 1. All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo) within each Study Group, with the exception of the site's pharmacy personnel.

Enrollment into all Study Groups will proceed in parallel. Once the first four (4) participants in Active Study Groups and the first two (2) participants in Placebo Study Groups have Week 2 clinical laboratory and adverse event data available, the results will be reviewed by the Data Safety and Monitoring Board (DSMB) (Figure 1). Enrollment will not be paused during this DSMB review, and screening and randomization may continue.

Upon completion of the Week 10 visit and availability of immunological data, Part 1 will be unblinded in order to allow for one regimen to be selected for advancement into Part 2. The Study Group with an optimal immune response, an acceptable safety profile and tolerant dosing regimen by Week 10, will be selected for Part 2. The Sponsor will remain blinded through Part 1 of the study until initiation of the Week 10 data review.

All Part 1 participants will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

Part 2 – Expansion

In Part 2, approximately 350 participants will be evaluated across one (1) dose level and regimen as outlined in Table 2 and Table 3. The dose level and regimen will be identified based on the optimal dose selection from Part 1. Enrollment into Part 2 may begin following completion of the Week 10 optimal dose and regimen selection in Part 1 (i.e., prior to Week 48 completion in Part 1).

Table 2: MERS-201 Part 2A Dose Groups

Study Group	Number of Participants	Dosing Weeks	Dose and Regimen
Active	300	0, 4 or 8	TBD
Placebo	50	0, 4 or 8	TBD
Total	**350**		

Table 3: MERS-201 Part 2B Dose Groups

Study Group	Number of Participants	Dosing Week	Dose and Regimen
Active – Booster	100[a]	48	TBD
Active – Placebo	100[b]	48	TBD
Placebo	25[c]	48	TBD
Total	**225**		

[a]First (Day 0), second (Week 4 or 8) and third (Week 48 booster) doses will be INO-4700.
[b]First (Day 0) and second (Week 4 or 8) doses will be INO-4700. Third dose will be a placebo dose at Week 48.
[c]Placebos will also receive a third dose in order to maintain blinded design. First (Day 0), second (Week 4 or 8) and third (Week 48) doses will be a placebo dose.
TBD, to be determined based on Part 1 optimal dose and regimen selection

In Part 2A, participants will be randomized to receive the optimal dose of active (INO-4700) selected in Part 1 of this study or placebo (SSC-0001) (Figure 1). Approximately 300 participants will receive INO-4700 and 50 participants will receive placebo.

In Part 2B, the first 200 participants are randomized to the Part 2A Active Study Group will receive a third dose of either INO-4700 or placebo at Week 48. Specifically, Study Group "Active – Booster" will receive INO-4700 at the first (Day 0), second (Week 4 or 8) and third (booster at Week 48) doses. Study Group "Active – Placebo" will receive INO-4700 at the first (Day 0)

and second (Week 4 or 8) doses, and placebo at the third (Week 48) dose. Similarly, in Part 2B, the first 25 participants randomized to the Part 2A Placebo Study Group will receive a third dose of placebo at Week 48. Collectively, these first 225 participants will be followed for 68 weeks from the Day 0 dosing [i.e., Week 68 will be the planned End of Study (EOS) visit]. All remaining 125 participants in Part 2A (i.e., those receiving only 2 doses) will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo), with the exception of the site's pharmacy personnel. Enrollment into Active and Placebo Study Groups will proceed in parallel. No enrollment pauses are planned.

Upon completion of the Week 12 visit and availability of immunological data, group-level (INO-4700 or placebo) unblinded summaries of immunogenicity and safety will be produced. This Week 12 analysis will serve to inform product development goals. The Sponsor will continue to remain blinded to subject-level treatment allocation (i.e., INO-4700 or placebo) for the remainder of the trial.

DSMB for Parts 1 and 2

The DSMB will remain unblinded throughout the duration of the study.

In Part 1, the DSMB will review clinical laboratory and adverse event data for the first six (6) participants, 4 active and 2 placebos, in each Active and Placebo Study Group, respectively, once the Week 2 safety data are complete. The DSMB will again convene to review all available safety data for all Study Groups once approximately 50% of planned participants are enrolled (i.e., approximately 96 participants), and once enrollment is complete.

Subsequently, the DSMB will convene every three (3) calendar months thereafter until study completion. Enrollment pauses are not planned during any DSMB review in Part 1 nor 2.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

Criteria for Evaluation:

Research Hypothesis:

- A selected optimal dose of INO-4700 delivered ID followed by EP using CELLECTRA™ 2000 in healthy volunteers will be well tolerated, exhibit an acceptable safety profile and result in generation of immune responses to MERS-CoV.

Primary Objectives:

- Evaluate the tolerability and safety of INO-4700 administered by ID injection followed by EP in healthy adult volunteers
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for identification and confirmation of an optimal dose and regimen
- Evaluate selected optimal dose for safety and immunogenicity

Primary Safety Endpoints:

- Incidence of adverse events by system organ class (SOC), preferred term (PT), severity and relationship to investigational product
- Administration (i.e., injection) site reactions (described by frequency and severity)
- Incidence of adverse events of special interest

Primary Immunogenicity Endpoints:

- Overall immune response
  - MERS-CoV antigen specific antibodies
  - Antigen specific cytokine-producing T cell responses

Exploratory Objective:

- Evaluate the expanded immunological profile by assessing both T and B cell immune responses
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for impact of boosting with a third dose

Exploratory Endpoint:

- Expanded immunological profile which may include (but not limited to) additional assessment of T and B cell numbers and T and B cell molecular changes by measuring immunologic proteins and mRNA levels of genes of interest at all weeks as determined by sample availability

Safety Assessment:

For Part 1, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6, Week 10 and Week 48. For Part 2, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details.

For both Parts 1 and 2, all adverse events, regardless of relationship, will be collected from the time of consent to 12 weeks from Day 0. Only related adverse events, adverse events of special interest and serious adverse events will be collected thereafter.

Additionally, for both Parts 1 and 2, a pregnancy test will be performed at screening and prior to each dose.

Immunogenicity Assessment:

For Part 1, immunology blood samples will be collected at Screening, Day 0, Week 2, Week 6, Week 10, Week 12 and Week 48. For Part 2, immunology blood samples will be collected at Screening, Day 0, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 12, Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details. Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

Clinical Trial Population:

Part 1 – Healthy adult volunteers between the ages of 18-50 years, inclusive.

Part 2 – Healthy adult volunteers at least 18 years of age.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. For Part 1, adults age 18 and 50 years, inclusive. For Part 2, adults at least 18 years of age;
c. Judged to be healthy by the Investigator on the basis of medical history, physical examination and vital signs performed at Screening; **Note:** Participants taking daily prescription or non-prescription medications for management of acceptable chronic medical conditions must be on a stable dose, as defined by non-change in dose for the 3 months prior to the first dose of study medication and no planned changes during the active dosing period of the study;
d. Able and willing to comply with all study procedures;
e. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
f. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening;
g. Screening ECG deemed by the Investigator as having no clinically significant findings (e.g. Wolff-Parkinson-White syndrome);
h. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or have a partner who is sterile (i.e., vasectomy in males at least six (6) months prior to enrollment or tubal ligation, absence of ovaries and/or uterus in females);
    - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 1 month 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. Pregnant or breastfeeding, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit until 1 month following last dose;
b. Positive serum pregnancy test during screening or positive urine pregnancy test prior to dosing;
c. History of respiratory diseases such as asthma, chronic obstructive pulmonary disease or chronic bronchitis;
d. Is currently participating in or has participated in a study with an investigational product with 30 days preceding Day 0;
e. Previous receipt of an investigational vaccine product for prevention of MERS or SARS;
f. Prior exposure to MERS-CoV or camels (serology or antibody testing will be requested at the Investigator's discretion);
g. Participants who participated in MERS-201 Part 1 cannot participate in MERS-201 Part 2;

h. Fewer than two acceptable sites available for ID injection and EP considering 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. Prisoner or participants who are compulsorily detained (involuntary incarceration);
j. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids) prior to dosing. Systemic corticosteroids must be discontinued at least 3 months prior to first dose;
k. Reported active drug or alcohol or substance abuse or dependence.

Clinical Trial Treatment:

- Part 1 Group A – One 0.6 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group B – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group C – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group D – Two 0.5 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group E – Two 1.0 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group F – One ID injection of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group G – One ID injection of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group H – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group I – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 2 – Dose and regimen to be determined, each ID injection(s) followed by EP administered at Day 0, Week 4 or Week 8, and Week 48 (for Part 2B participants receiving a third dose)

INO-4700 or placebo will be administered intradermally in ~0.1 mL dose volume followed immediately by EP.

Formulation:

INO-4700 in sodium chloride and sodium citrate, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

FIGURE 1 – STUDY DESIGN AND DOSING SCHEMA

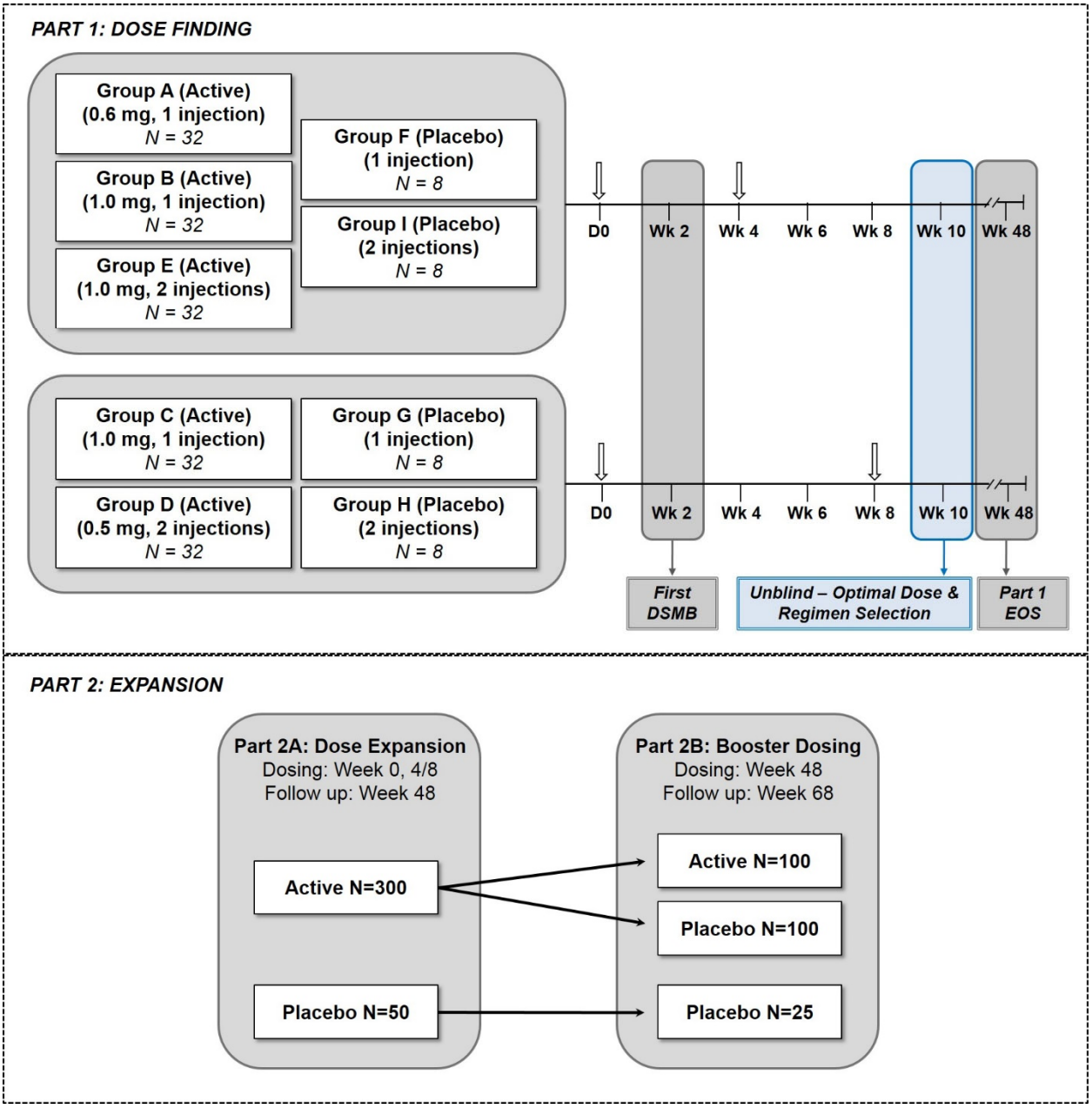


TABLE 4 – PART 1 TRIAL SCHEDULE OF EVENTS

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4 (± 5d)		Week 6 (± 5d)	Week 8 (± 5d)		Week 10 (± 5d)	Week 12 (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)
		Pre	Post		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
Physical Exam[c]	X	X		X	X		X	X		X			X
Vital Signs	X	X		X	X		X	X		X			X
Height and Weight	X												
CBC with Differential	X			X			X			X			X
Chemistry and Liver Function[d]	X			X			X			X			X
Serology[e]	X												
12-lead ECG	X												
Urinalysis Routine[f]	X			X			X			X			X
Pregnancy Test[g]	X	X			X[k]			X[l]					
INO-4700 or placebo + EP[h]		X[i,j]			X[i,k]			X[j,l]					
Download EP Data[m]			X			X[k]			X[l]				
Adverse Events[n]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology (Whole blood)[o]	X	X		X			X			X	X		X
Immunology (Serum)[p]	X	X		X			X			X	X		X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs
c. Full physical examination at screening and Week 48 (or any other study discontinuation visit) only. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. For Study Groups A, B and F, one injection preferably over deltiod muscle at Day 0 and Week 4. For Study Groups E and I, two injections with each injection over a different deltoid or lateral quadriceps, preferably over the deltoid muscles, at Day 0 and Week 4.
j. For Study Groups C and G, one injection preferably over deltoid muscle at Day 0 and Week 8. For Study Groups D and H, two injections with each injection over a different deltoid or lateral quadriceps, preferably over the deltoid muscles, at Day 0 and Week 8.
k. Complete only for Study Groups A, B, E, F and I.
l. Complete for Study Groups C, D, G and H.
m. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
n. Includes AEs from the time of consent and all injection site reactions that qualify as an AE. All AEs collected until 12 weeks from Day 0. Related AEs, AESIs and SAEs collected thereafter.
o. 4 x 8.5 mL (34 mL) whole blood in 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 (screening and prior to Day 0 dosing).
p. 1 x 8 mL blood in 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).

TABLE 5 – PART 2 TRIAL SCHEDULE OF EVENTS (DAY 0 & WEEK 4 OPTIMAL REGIMEN)

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4 (± 5d)		Week 6 (± 5d)	Week 8[b] (± 5d)	Week 12 (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)		Week 50[i] (± 5d)	Week 68[i] (± 10d)
		Pre	Post		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
Physical Exam[c]	X	X		X	X		X				X		X	X
Vital Signs	X	X		X	X		X				X		X	X
Height and Weight	X													
CBC with differential	X			X			X				X		X	X
Chemistry and Liver Function[d]	X			X			X				X		X	X
Serology[e]	X													
12-lead ECG	X													
Urinalysis Routine[f]	X			X			X				X		X	X
Pregnancy Test[g]	X	X			X						X[i]			
INO-4700 or placebo + EP[h]	X	X			X						X[i]			
Download EP Data[j]			X			X						X[i]		
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X
Immunology (Whole blood)[l]	X	X		X			X		X		X		X	X
Immunology (Serum)[m]	X	X		X			X		X		X		X	X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs.
c. Full physical examination at screening and Week 48 (participants receiving only two doses) or Week 68 (participants receiving three doses), as well as any other study discontinuation visit. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test prior to dosing at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. Complete only for participants receiving a third dose of either INO-4700 or placebo (Part 2B).
j. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
k. Includes AEs from the time of consent and all injection site reactions that qualify as an AE. All AEs collected until 12 weeks from Day 0. Related AEs, AESIs and SAEs collected thereafter.
l. 4 x 8.5 mL (34 mL) whole blood in 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 (screening and prior to Day 0 dosing).
m. 1 x 8 mL blood in 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).

TABLE 6 – PART 2 TRIAL SCHEDULE OF EVENTS (DAY 0 & WEEK 8 OPTIMAL REGIMEN)

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4[b] (± 5d)	Week 8 (± 5d)		Week 10 (± 5d)	Week 12 (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)		Week 50[i] (± 5d)	Week 68[i] (± 10d)
		Pre	Post			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
Physical Exam[c]	X	X		X		X		X			X		X	X
Vital Signs	X	X		X		X		X			X		X	X
Height and Weight	X													
CBC with differential	X			X				X			X		X	X
Chemistry and Liver Function[d]	X			X				X			X		X	X
Serology[e]	X													
12-lead ECG	X													
Urinalysis Routine[f]	X			X				X			X		X	X
Pregnancy Test[g]	X	X				X					X[i]			
INO-4700 or placebo + EP[h]	X	X				X					X[i]			
Download EP Data[j]			X				X					X[i]		
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X
Immunology (Whole blood)[l]	X	X		X				X	X		X		X	X
Immunology (Serum)[m]	X	X		X				X	X		X		X	X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs.
c. Full physical examination at screening and Week 48 (participants receiving only two doses) or Week 68 (participants receiving three doses), as well as any other study discontinuation visit. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test prior to dosing at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. Complete only for participants receiving a third dose of either INO-4700 or placebo (Part 2B).
j. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
k. Includes AEs from the time of consent and all injection site reactions that qualify as an AE. All AEs collected until 12 weeks from Day 0. Related AEs, AESIs and SAEs collected thereafter.
l. 4 x 8.5 mL (34 mL) whole blood in 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 (screening and prior to Day 0 dosing).
m. 1 x 8 mL blood in 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).

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 indicates that MERS-CoV infection remains a serious unmet medical need. Due to cross-species infection, both human and animal outbreaks are possible. Appropriate measures to prevent, control and treat existing and future infections are needed.

1.2 BACKGROUND INFORMATION

First reported in 2012 in a patient from Saudi Arabia presenting with pneumonia and acute kidney injury, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was originally known as coronavirus-EMS (Erasmus Medical Center) [1]. Although only more recently has human infection been identified, evidence suggests that MERS-CoV has existed in central and east Africa for decades [2]. MERS-CoV belongs to the family *Coronaviridae*, which includes four major groups: alpha, beta, gamma and delta. Although genomically related to the subgroup B beta-coronavirus severe acute respiratory syndrome (SARS) virus, MERS-CoV belongs to the subgroup C beta-coronavirus lineage. Two main recognized clades (clade A and B) of MERS-CoV have been identified by phylogenetic analysis, of which clade B can be further subdivided into five groups (groups I, II, III, IV, V). As a novel beta-coronavirus with high pathogenicity, significant morbidity and mortality is associated with infection of this subgroup, in contrast to less severe illness with other coronavirus infection [3].

Based on analyses of MERS-CoV's evolutionary history, natural hosts include bats *(species Neoromicia capensis* and *Vespertilio superans*), dromedary camel (*Camelus dromedarius*) and European hedgehog (*Erinaceus europaeus)* [4-7]. Its high recombination potential and evasion of host immune responses provides coronaviruses the ability to infect multiple host species, thus supporting the contribution of zoonotic events to adaptive evolution and disease transmission. Notably, dromedary camels are the only documented cross-species source for human infection [8]. However, the mechanism by which transmission occurs from natural animal hosts to human is still poorly characterized [9].

Those in a healthcare setting or who have come into contact with camels constitute the majority of known exposure routes and potential source of transmission [10]. Indeed, nosocomial transmission due to inadequate infection control has been established as a major driver of MERS-CoV infections in humans [11, 12], and contributed to the 2014 outbreak in Saudi Arabia and 2015 outbreak in South Korea. Primary cases tend to be middle-aged males and those with occupational exposure to animal hosts, while secondary cases include younger men and women and those who've come into contact with confirmed patients.

1.2.1 CLINICAL PRESENTATION AND IMMUNE RESPONSE

The incubation period for MERS-CoV is about 5-7 days and can be up to 12 days. MERS-CoV infection causes lower respiratory tract disease due to the highly susceptible nature of respiratory epithelial cells [13]. As such, greater viral loads are detected in the lower respiratory tract compared to the upper tract. Renal, intestinal and liver cells and

histiocytes can also be affected. Most common symptoms include fever, cough, shortness of breath and pneumonia, but myalgia, diarrhea, vomiting, chills and malaise have also been observed [10, 14]. Severe infection has been associated with acute kidney damage and respiratory distress requiring intensive care unit management within 2 days of hospital admission and can progress to multiorgan system failure [15]. Symptomatic patients carry MERS-CoV in tracheal aspirates, sputum and bronchoalveolar lavage fluid, and due to continuous viral shedding up to six weeks, patients may be able to transmit virus even when asymptomatic [16]. Poorer disease outcome and higher mortality may occur in older or immunocompromised patients and those with comorbidities, such as diabetes, cancer, and cardiac and chronic pulmonary disease [17].

Multiple studies suggest that host immune function and kinetics are important factors in determining disease course. Although higher antibody titers in correlation with greater viral load and delayed development of neutralizing antibodies were associated with poorer prognosis, the protective effect of these antibodies during infection is not clear [18, 19]. Additionally, both duration and magnitude of antibody response is indicative of disease severity [20]. From a cellular immunity perspective, MERS-CoV may downregulate expression of interferon-stimulated genes and delay induction of proinflammatory cytokines. Cytotoxic T cells are implicated in host defense and recovery as one study reported $CD8^+$ T cell responses in survivors despite the lack of an antibody response [18].

1.2.2 CURRENT TREATMENT AND UNMET NEED

Current treatment focuses on symptomatic supportive care. Ribavirin and IFN-α2b administration have been shown to decrease viral replication *in vitro*, improve outcomes in animals and increase short-term survival in a retrospective human study [21, 22]. Ribavirin and IFN-α2b in combination with lopinavir is currently being tested in an interventional Phase 2 clinical trial (clinicaltrials.gov NCT02845843).

Other targets in development include viral and host proteases and viral entry inhibitors, such as inhibition of dipeptidyl-peptidase 4 (DPP4 or CD26) on the host cell. DPP4 acts as the main route of entry utilized by the virus' spike (S) protein, which is the primary target for neutralizing antibodies. Specifically, two monoclonal antibodies (REGN3051 and REGN3048) are able to bind the receptor binding domain (RBD) region within the S protein with high affinity and neutralize MERS-CoV *in vitro* [23]. In mouse models, these antibodies act as inhibitors against the DPP4 and S protein interaction and have shown effectiveness in restricting MERS-CoV replication and infection [23, 24]. Additional monoclonal antibodies, all targeting RBD, are being developed by several groups [25].

Importantly, vaccines have been prioritized as a promising alternative. Currently, there are no approved prophylactic nor therapeutic vaccines available for the prevention and treatment of MERS-CoV infection. Vaccine development for MERS-CoV may be challenging due to the sporadic nature of infection and lack of suitable animal models for challenge studies. Additionally, determinants of protection and immunity are not clearly defined. Development of both viral vector-based and RBD-based formats are ongoing. Replication deficient modified vaccinia Ankara (MVA) expressing full-length MERS-CoV spike protein and adenovirus vectors have demonstrated humoral and cellular immune responses, but adverse inflammation and safety remain a concern [26]. A live-attenuated MERS-CoV vaccine also exists but would require higher biosafety precautions for testing and would not be feasible for the target population more prone to severe MERS-CoV disease [27]. RBD-based vaccines are proposed to be more effective and safer than viral vector-based vaccines. Intranasal RBD-based immunization in animals elicits strong mucosal IgA responses as well as specific cell-mediated responses that may contribute to protection [28, 29]. Combination with adjuvants, such as aluminum or oil-based MF59,

has potential to increase effectiveness. However, evaluation of vaccine candidates in humans must be performed to better inform efficacy, and a vaccination platform that induces both humoral and cellular immune response could be rationalized.

Multiple vaccine platforms are in various preclinical testing stages [25], with a few vaccine candidates advancing into Phase 1 clinical testing. GLS-5300 (GeneOne Life Science, Inc.), which is comprised of an identical DNA plasmid as INO-4700, is a DNA-based vaccine targeting MERS-CoV S protein and has been evaluated in a completed Phase 1 intramuscular dose-ranging study in healthy adults (clinicaltrials.gov NCT02670187) [30], described further in Section 1.3.1. A second, Phase 1/2a study of GLS-5300 is ongoing to evaluate the safety and immunogenicity of intradermal administration (clinicaltrials.gov NCT03721718), described further in Section 1.3.1. Preclinical studies of GLS-5300 in mice, camels and non-human primates (NHPs) have demonstrated induction of neutralizing antibodies and antigen-specific cellular immune responses. Of note, vaccination in NHPs was able to protect from MERS-CoV challenge as immunized animals lacked respiratory distress and interstitial infiltrates, had normal lung histology and cleared viral loads [31].

1.2.3 EMERGING HEALTH THREAT

Since 2012, the World Health Organization (WHO) has received over 2,400 laboratory-confirmed reports of individual cases and clusters of infection, including over 800 fatalities, across 27 countries (Saudi Arabia accounting for 80% of human cases) [32]. The latest WHO-reported crude fatality rate is 35.5% [33]. Although the majority of research has focused on symptomatic patients, more than 62% of these individuals may remain unidentified or undetected or display only mild symptoms [34], thus the number of confirmed cases may be greatly under-reported. Not only is continued development of enhanced detection and active surveillance programs warranted, but also more effective therapeutic options are required to manage existing infections and limit spread of disease. In support of continued advancements to address this serious global health concern, the Coalition for Epidemic Preparedness Innovations (CEPI) has assigned priority disease designation to developing a MERS-CoV vaccine [35], and the WHO has initiated a blueprint for preparatory and responses efforts [36].

1.3 RATIONALE

No investigational interventions have clearly and consistently demonstrated clinical benefit in MERS-CoV-infected patients, thus highlighting the continued unmet need for effective therapeutic and preventive solutions. INO-4700 is being evaluated for both routine prophylaxis and use during an outbreak situation. Since the RBD domain within the MERS-CoV S protein is highly mutable, INO-4700 has been designed to encode consensus sequences of the full length S protein covering multiple epitopes in order to induce broad cross-reactive immune responses. The INO-4700 plasmid, which is identical to GLS-5300, and the plasmid DNA backbone has been tested in previous clinical trials [30, 37-40]. Previous experience with plasmids similar to INO-4700 has demonstrated tolerability and both clinically relevant and immunogenic responses.

1.3.1 DOSE AND REGIMEN RATIONALE

INO-4700 is identical to the previously evaluated GLS-5300, except that it is formulated at a higher concentration. In a completed Phase 1 clinical trial, intramuscular (IM) dose-ranging administration of GLS-5300 delivered via EP in healthy adults was well-tolerated and induced seroconversion and T cell responses [30]. This study evaluated three different dose groups (0.67 mg, 2 mg, and 6 mg) administered IM in a three-immunization regimen

at Weeks 0, 4 and 12 in 75 healthy adult participants. Overall, transient local injection site discomfort and reactions were most commonly reported, consistent with previously published clinical trial reports of Inovio's DNA delivered via EP platform. The most common solicited systemic adverse event was headache, followed by malaise and myalgia, most of which were mild. Laboratory abnormalities were uncommon, and no grade 3 or higher laboratory abnormalities were deemed related to the vaccine. No vaccine-related serious adverse events were reported. The vaccine was immunogenic in all dosing groups with remarkably similar antibody and neutralization titers between all three doses. These levels were comparable to those observed in convalescent patients who have recovered from MERS-CoV infection. Furthermore, the vaccine generated long-lasting T cell responses that maintained average levels higher than convalescent patients for at least 60 weeks. Flow cytometry analysis and intracellular cytokine staining detected increases in $CD8^+$ T cells secreting IFNγ and TNFα and $CD4^+$ T cells secreting TNFα. In summary, the data from this first Phase 1 trial supports the strong immunogenicity of the vaccine and ability to induce durable immune responses for at least 1 year.

In an ongoing Phase 1/2a dose-ranging clinical trial, the safety, tolerability and immunogenicity of GLS-5300 delivered intradermally (ID) followed by EP in 60 healthy volunteers is being evaluated. Dose levels include 0.3 mg administered in a three-immunization regimen at Week 0, 4 and 12, 0.6 mg administered in a three-immunization regimen at Week 0, 4 and 12, and 0.6 mg administered in a two-immunization regimen at Week 0 and 8. As of June 2019, there have been no reports of treatment-associated serious adverse events and the majority of adverse events reported have been grade 1 or grade 2 in severity. Adverse event data standardization is in progress, but the most commonly reported adverse events are similar to that reported in the completed Phase 1 trial.

An interim analysis has showed that ID delivery of GLS-5300 induced a robust binding antibody and IFNγ cellular immune response in humans. A dose response was observed, such that the 0.6 mg dose induced significantly higher humoral and cellular immune responses. The 0.6 mg dose induced up to a 76% seroconversion rate following a single immunization, 88% seroconversion following the second immunization, and 100% seroconversion following the third. The 0.6 mg dose also induced robust cellular immune responses, with 56% responders after the second immunization and 78% responders after the third. The two-immunization regimen (Week 0 and 8 dosing) appeared to induce significantly higher antibody titers than the three-immunization regimen (Week 0, 4 12) as early as 2 weeks post second immunization, without affecting the cellular immune response. The overall response rate for the 0.6 mg dose, three-immunization regimen reached 92% after two immunizations and increased to 100% following the third immunization. The 0.6 mg dose, two-immunization regimen reached an overall response rate of 96% after only two immunizations.

Results from the complete Phase 1 clinical trial as well as interim safety and immunogenicity results from the ongoing Phase 1/2a clinical trial support continued evaluation of this plasmid in a demographically relevant population.

Intradermal delivery has been shown to be a more tolerable route of administration that induces superior humoral immune responses for previously evaluated DNA vaccines targeting viruses such as Ebola, Zika and HIV [39-41].

As such, Part I of the current clinical trial represents the dose-finding phase of the study to supplement previously amassed safety and immunogenicity data. Participants in Part 1 will receive dosing on Day 0 and Week 4 or Week 8, with a starting dose of INO-4700 of

0.6 mg, which demonstrated robust immunogenicity in the Phase 1/2a trial of GLS-5300 delivered ID followed by EP.

Furthermore, a long-term kinetic study of serologic responses from patients who recovered during the 2015 South Korea outbreak reports more rapid waning of antibody response during the first 6 months of disease onset that stabilizes between 6 months to 1 year [42]. Similarly, a study of survivors from the 2014 Saudi Arabia outbreak reports fewer patients with positive antibody response at 10 months following disease onset compared to 3 months [43]. As this data may indicate variable response over time, participants in Part 2 will receive dosing on Day 0 and Week 4 or 8 and a booster dose at Week 48 (only for the first 225 participants). Part 2 will thus confirm the optimal dose identified in Part 1 and will serve to also evaluate the impact of a booster/third dose.

Based on the at-risk population, active immunization should demonstrate ability to drive clinically relevant immune responses within 4-6 weeks of administration with long-term protection. Additionally, the WHO target product profile for a MERS-CoV vaccine suggests dosing regimens of no more than 3 doses in prophylactic settings and no more than 2 doses in reactive settings, with short intervals between doses [44].

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 [45-54]. 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 [53, 55] In many cases, protection from disease in animal models has also been demonstrated.

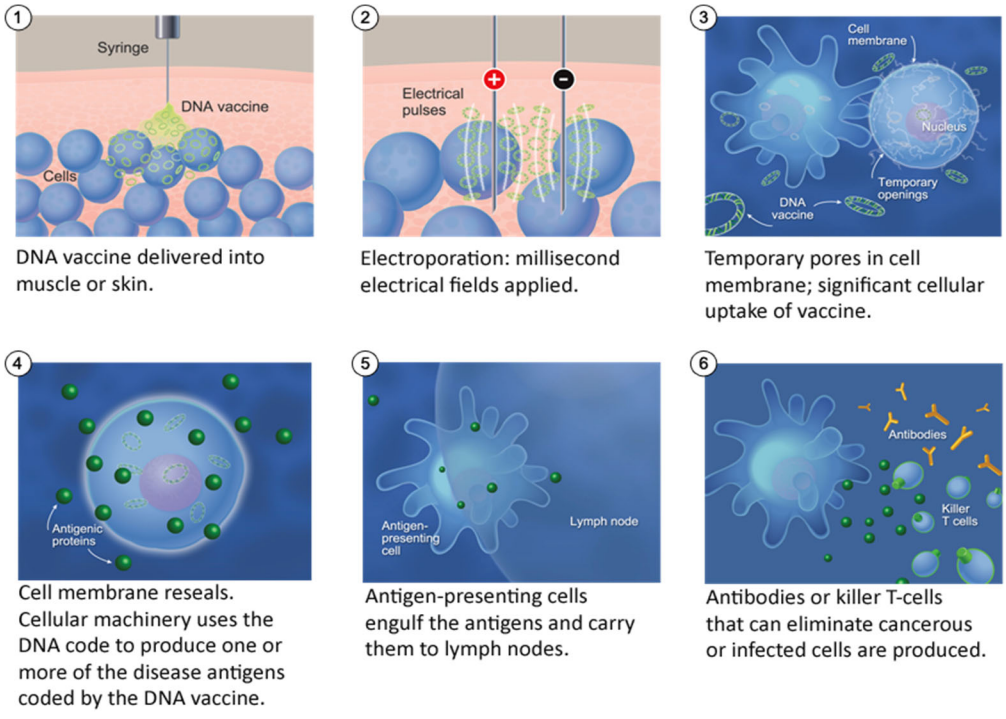
DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses 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 [56]. 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. 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 [57]. 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 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 [58]. 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 [58] for the activation of both cellular and humoral responses [59, 60]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [60]. 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 [61, 62].

The Inovio Pharmaceuticals constant current EP device [58] 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-4700 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) [40].

Figure 2: How Electroporation Works in the Body



1.4 POTENTIAL BENEFITS AND RISKS

As of September 30 2019, a total of 75 participants have been dosed with INO-4700 IM and 60 participants with INO-4700 ID. In studies of INO-4700 administered IM followed by EP using CELLECTRA™ 2000 devices in healthy volunteers the most frequently reported AE has been injection site pain (94.7%), of which all were Grade 2 or less. In the ongoing

study of INO-4700 administered ID followed by EP using CELLECTRA™ 2000 devices in healthy volunteers, the most frequently reported AE has been erythema (63.3%), of which all were Grade 1 (taken from unvalidated data as a preliminary analysis).

No specific AE has been identified as a risk. There may be potential benefit for prevention of MERS infection in affected areas, but efficacy is still unknown. Data gathered in this trial will be useful for future development of this vaccine for MERS-CoV.

Additional details regarding the benefits and risks for participants 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 INO-4700 in a demographically relevant population with the eventual goal of preparation for both routine prophylaxis and use during an outbreak situation.

2.1 HYPOTHESIS

A selected optimal dose of INO-4700 delivered ID followed by EP using CELLECTRA™ 2000 in healthy volunteers will be well tolerated, exhibit an acceptable safety profile and result in generation of immune responses to MERS-CoV.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is a Phase 2a, randomized, blinded, placebo-controlled, multi-center trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered by ID injection followed by EP using the CELLECTRA™ 2000 device in healthy adult volunteers. The primary objectives of this trial are to evaluate the tolerability, safety and immunogenicity of INO-4700 administered by ID injection followed by EP in healthy adult volunteers according to the regimens outlined in Table 1, Table 2, Table 3 and Figure 1.

Approximately 542 healthy volunteers will be evaluated across two (2) parts of this study, Part 1 and Part 2. INO-4700 or placebo (SSC-0001) will be administered ID in ~0.1 mL dose volume followed immediately by EP.

Part 1 – Dose Finding

In Part 1, approximately 192 participants ages 18-50 years will be assessed through five (5) dose levels and regimens. These five (5) dose levels and regimens will be evaluated across nine (9) groups designated Study Groups A, B, C, D, E, F, G, H and I. Study Groups A, B, C, D and E will receive INO-4700 and enroll approximately 32 participants per group. Study Groups F, G, H and I will receive placebo and enroll approximately 8 participants per group.

Participants will be randomized to receive either INO-4700 or placebo according to the dosing schedule described in Table 1. All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo) within each Study Group, with the exception of the site's pharmacy personnel.

Enrollment into all Study Groups will proceed in parallel. Once the first four (4) participants in Active Study Groups and the first two (2) participants in Placebo Study Groups have Week 2 clinical laboratory and adverse event data available, the results will be reviewed by the DSMB (Figure 1). Enrollment will not be paused during this DSMB review, and screening and randomization may continue.

Upon completion of the Week 10 visit and availability of immunological data, Part 1 will be unblinded in order to allow for one regimen to be selected for advancement into Part 2. The Study Group with an optimal immune response, an acceptable safety profile and tolerant dosing regimen by Week 10 will be selected for Part 2. The Sponsor will remain blinded through Part 1 of the study until initiation of the Week 10 data review.

All Part 1 participants will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

Part 2 – Expansion

In Part 2, approximately 350 participants will be evaluated across one (1) dose level and regimen as outlined in Table 2 and Table 3. The dose level and regimen will be identified based on the optimal dose selection from Part 1. Enrollment into Part 2 may begin following completion of the Week 10 optimal dose and regimen selection in Part 1 (i.e., prior to Week 48 completion in Part 1).

In Part 2A, participants will be randomized to receive the optimal dose of active (INO-4700) selected in Part 1 of this study or placebo (SSC-0001) (Figure 1). Approximately 300 participants will receive INO-4700 and 50 participants will receive placebo.

In Part 2B, the first 200 participants randomized to the Part 2A Active Study Group will receive a third dose of either INO-4700 or placebo at Week 48. Specifically, Study Group "Active – Booster" will receive INO-4700 at the first (Day 0), second (Week 4 or 8) and third (booster at Week 48) doses. Study Group "Active – Placebo" will receive INO-4700 at the first (Day 0) and second (Week 4 or 8) doses, and placebo at the third (Week 48) dose. Similarly, in Part 2B, the first 25 participants randomized to the Part 2A Placebo Study Group will receive a third dose of placebo at Week 48. Collectively, these first 225 participants will be followed for 68 weeks from the Day 0 dosing [i.e., Week 68 will be the planned End of Study (EOS) visit]. All remaining 125 participants in Part 2A (i.e., those receiving only 2 doses) will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo), with the exception of the site's pharmacy personnel. Enrollment into Active and Placebo Study Groups will proceed in parallel. No enrollment pauses are planned.

Upon completion of the Week 12 visit and availability of immunological data, group-level (INO-4700 or placebo) unblinded summaries of immunogenicity and safety will be produced. This Week 12 analysis will serve to inform product development goals. The Sponsor will continue to remain blinded to subject-level treatment allocation (i.e., INO-4700 or placebo) for the remainder of the trial.

DSMB for Parts 1 and 2

The DSMB will remain unblinded throughout the duration of the study.

In Part 1, the DSMB will review clinical laboratory and adverse event data for the first six (6) participants, 4 active and 2 placebos, in each Active and Placebo Study Group, respectively, once the Week 2 safety data are complete. The DSMB will again convene to review all available safety data for all Study Groups once approximately 50% of planned participants are enrolled (i.e., approximately 96 participants), and once enrollment is complete.

Subsequently, the DSMB will convene every three (3) calendar months thereafter until study completion. Enrollment pauses are not planned during any DSMB review in Part 1 nor 2.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified immediately, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

3.1 PRIMARY OBJECTIVES

- Evaluate the tolerability and safety of INO-4700 administered by ID injection followed by EP in healthy adult volunteers
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for identification and confirmation of an optimal dose and regimen
- Evaluate selected optimal dose for safety and immunogenicity

3.2 PRIMARY ENDPOINTS

Safety Endpoints:

- Incidence of adverse events by system organ class (SOC), preferred term (PT), severity and relationship to investigational product
- Administration (i.e., injection) site reactions (described by frequency and severity)
- Incidence of adverse events of special interest

Immunogenicity Endpoints:

- Overall Immune response
  - MERS-CoV antigen specific antibodies
  - Antigen-specific cytokine-producing T cell responses

3.3 EXPLORATORY OBJECTIVE

- Evaluate the expanded immunological profile by assessing both T and B cell immune responses
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for impact of boosting with a third dose

3.4 EXPLORATORY ENDPOINT

- Expanded immunological profile which may include (but not limited to) additional assessment of T and B cell numbers and T and B cell molecular changes by measuring immunologic proteins and mRNA levels of genes of interest at all weeks as determined by sample availability

3.5 SAFETY ASSESSMENT

For Part 1, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6, Week 10 and Week 48. For Part 2, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 48, Week 50 (for participants receiving three doses) and Week 68 (for participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details.

For both Parts 1 and 2, all adverse events, regardless of relationship, will be collected

from the time of consent to 12 weeks from Day 0. Only related adverse events, AESIs, and serious adverse events will be collected thereafter.

Additionally, for both Parts 1 and 2, a pregnancy test will be performed at screening and prior to each dose.

3.6 IMMUNOGENICITY ASSESSMENT

For Part 1, immunology blood samples will be collected at Screening, Day 0, Week 2, Week 6, Week 10, Week 12 and Week 48. For Part 2, immunology blood samples will be collected at Screening, Day 0, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 12, Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details. Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

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. For Part 1, adults age 18 and 50 years, inclusive. For Part 2, adults at least 18 years of age;
c. Judged to be healthy by the Investigator on the basis of medical history, physical examination and vital signs performed at Screening. **Note:** Participants taking daily prescription or non-prescription medications for management of acceptable chronic medical conditions must be on a stable dose, as defined by non-change in dose for the 3 months prior to the first dose of study medication and no planned changes during the active dosing period of the study;
d. Able and willing to comply with all study procedures;
e. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
f. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening;
g. Screening ECG deemed by the Investigator as having no clinically significant findings (e.g. Wolff-Parkinson-White syndrome);
h. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or have a partner who is sterile (i.e., vasectomy in males at least six (6) months prior to enrollment or tubal ligation, absence of ovaries and/or uterus in females);
    - Use of medically effective contraception with a failure rate of < 1% per year when used consistently and correctly from screening until 1 month 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. Pregnant or breastfeeding, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit until 1 month following last dose;
b. Positive serum pregnancy test during screening or positive urine pregnancy test prior to dosing;
c. History of respiratory diseases such as asthma, chronic obstructive pulmonary disease or chronic bronchitis;
d. Is currently participating in or has participated in a study with an investigational product with 30 days preceding Day 0;
e. Previous receipt of an investigational vaccine product for prevention of MERS or SARS;
f. Prior exposure to MERS-CoV or camels (serology or antibody testing will be requested at the Investigator's discretion);
g. Participants who participated in MERS-201 Part 1 cannot participate in MERS-201 Part 2;
h. Fewer than two acceptable sites available for ID injection and EP considering 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. Prisoner or participants who are compulsorily detained (involuntary incarceration);
j. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids) prior to dosing. Systemic corticosteroids must be discontinued at least 3 months prior to first dose;
k. Reported active drug or alcohol or substance abuse or dependence.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL PARTICIPANTS

Participants 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 withdraw 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 discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Part 1 Week 48 EOS or Part 2 Week 48 or 68 EOS) should be performed at the time of discontinuation. Any AEs 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: Safety Data Reporting Period, Method of Collection and Submission.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Tables 3, 4 and 5) following the last dose whether or not the subject has completed all doses.

Reasons for 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 participants who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate eCRF. However, participants 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.

Subject dosing may be discontinued if they experience any of 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 TREATMENT

5.1 INVESTIGATIONAL PRODUCTS (IPS) AND STUDY DEVICE

5.1.1 INO-4700 AND SSC-0001

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-4700 is the active investigational product to be used in this study. The INO-4700 drug product contains 10 mg/mL pGX9101 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps. INO-4700 must be placed in 2–8°C storage immediately upon arrival and requires preparation prior to administration, which is outlined in the pharmacy manual.

pGX9101 is a DNA plasmid expressing a synthetic consensus (SynCon®) Middle East Respiratory Syndrome Human Coronavirus Spike protein (MERS-CoV Spike), driven by a human CMV promoter (hCMV promoter), and with the bovine growth hormone 3' end poly-adenylation signal (bGH polyA). The pGX0001 backbone includes the kanamycin resistance gene (KanR) and plasmid origin of replication (pUC ori).

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 at the clinical site.

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 TREATMENT REGIMENS

- Part 1 Group A – One 0.6 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group B – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group C – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group D – Two 0.5 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group E – Two 1.0 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group F – One ID injection of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group G – One ID injection of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group H – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group I – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 2 – Dose and regimen to be determined, each ID injection(s) followed by EP administered at Day 0, Week 4 or Week 8, and Week 48 (for Part 2B participants receiving a third dose)

INO-4700 or placebo will be administered intradermally in ~0.1 mL dose volume followed immediately by EP.

5.2.1 BLINDING

This trial is randomized across Study Groups, is blinded to the Investigator and subject, and is placebo-controlled with blinding throughout the duration of the trial as described in Section 3: Clinical Trial Design and Endpoints. There is no difference in appearance

between INO-4700 and SSC-0001; 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 Sponsor will also be blinded as described in Section 3: Clinical Trial Design and Endpoints.

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) with the study product 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-4700 / SSC-0001

This trial is randomized and blinded across study groups and placebo-controlled. Therefore, the subject and the Investigator's clinical site personnel (except for the site pharmacy) are blinded to INO-4700 and SSC-0001. Each vial of investigational product 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, and User Manual for unpacking instructions.

The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, potential risks and adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 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-4700 AND SSC-0001

INO-4700 and SSC-0001 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 unblinded 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-4700 is supplied in single dose 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-4700 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 fill INO-4700 or SSC-0001 into a blinded syringe in accordance with the subject's randomization code. The syringe will be transferred to blinded site personnel for administration. The preparation and dispensing information is provided in the Pharmacy Manual. A randomization schedule will be generated by the Sponsor statistician.

5.6 USE OF STUDY DEVICE

The CELLECTRA™ 2000 is an investigational 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 INO-4700 AND SSC-0001 ACCOUNTABILITY

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

5.7.2 CELLECTRA™ 2000 ACCOUNTABILITY

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

For each subject administration, there must be a record of each product used for that participant, i.e., CELLECTRA™ 2000 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-4700 AND SSC-0001

Upon completion or termination of the study, all unused IP (INO-4700 and SSC-0001) 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 IP vials 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. All precautions must be taken to maintain blind throughout this process. If requested by the Sponsor, the return of unused IP should be arranged by the responsible Inovio Representative. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. personnel or designated unblinded Clinical Monitor. If IP is 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 unblinded 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 trial Schedule of Events (Tables 4, 5 and 6) in the Clinical Protocol Synopsis summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. A 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 study 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. Participants' post-menopausal status must meet requirements as specified in the inclusion criteria [63, 64]. The following screening evaluations will be performed within 60 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration.

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

- Signed and dated informed consent (Section 6.2);
- Review and confirm all inclusion/exclusion criteria (Section 4.1 and 4.2);
- Obtain and document complete medical history, surgical history (including all past procedures), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics, including gender, 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 including body weight and height, heart rate (HR), respiratory rate (RR), blood pressure (BP) and oral temperature (Section 6.4);
- Collect blood for CBC with differential, serum chemistry (sodium [Na], potassium [K], chloride [Cl], bicarbonate [HCO_3], calcium [Ca], phosphate [PO_4], glucose, blood urea nitrogen [BUN] and creatinine [Cr]) and liver function [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] (Section 6.4);
- Perform 12 lead ECG (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for MERS-CoV (per PI discretion), HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C serology (Section 6.4) per national guidelines;
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

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 or new treatments taken at or after the signing of the informed consent, should be recorded in the CRF as concomitant medications.

6.1.2 CLINICAL TRIAL EVALUATIONS AND PROCEDURES

Once eligibility has been confirmed, the participant will be assigned to receive IP. Visit dates and windows must be calculated from Day 0, unless otherwise noted. All study groups in Part 1 will be followed until Week 48, booster dose participants in Part 2 will be followed to Week 68 and all other participants in Part 2 who did not receive booster dose will be followed to Week 48. All participants will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0

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

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- 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 immunology assessment (Section 6.4.6).

The following evaluation will be performed on **Day 0 prior to EP:**

- Assess for injection site for IP leakage (Section 6.4.1)

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

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

6.1.2.2 Week 2

Calculated from Day 0, the following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.3 Week 4

Part 1

The following evaluations will be performed on **Week 4 (complete prior to IP administration for Part 1 Study Groups A, B, E, F and I):**

- Collect all present and/or new or ongoing adverse events;
- 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) for Part 1 Study Groups A, B, E, F and I only.

The following evaluation will be performed on **Week 4 prior to EP (for Part 1 Study Groups A, B, E, F and I only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 4 after IP administration (for Part 1 Study Groups A, B, E, F and I only)**:

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

Part 2 if Day 0/Week 4 Dosing Regimen is Optimal

The following evaluations will be performed on **Week 4 (complete prior to IP administration if following Table 5):**

- Collect all present and/or new or ongoing adverse events;
- 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).

The following evaluation will be performed on **Week 4 prior to EP (if following Table 5 only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 4 after IP administration (if following Table 5 only)**:

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

Part 2 if Day 0/Week 8 Dosing Regimen is Optimal

The following evaluation will be collected on **Week 4 (if following Table 6 only)** during a follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

6.1.2.4 Week 6

Calculated from Week 4 if Week 4 is a dosing visit, the following evaluations will be performed at this visit for **Part 1 and Part 2 if Day 0/Week 4 dosing regimen is optimal**:

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function(Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.5 Week 8

Part 1

The following evaluations will be performed on **Week 8 (complete prior to IP administration for Part 1 Study Groups C, D, G and H):**

- Collect all present and/or new or ongoing adverse events;
- 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) for Part 1 Study Groups C, D, G and H only.

The following evaluation will be performed on **Week 8 prior to EP (for Part 1 Study Groups C, D, G and H only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 8 after IP administration (for Part 1 Study Groups C, D, G and H only)**:

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

Part 2 if Day 0/Week 4 Dosing Regimen is Optimal

The following evaluation will be collected on **Week 8 (if following Table 5 only)** during a follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

Part 2 if Day 0/Week 8 Dosing Regimen is Optimal

The following evaluations will be performed on **Week 8 (complete prior to IP administration if following Table 6):**

- Collect all present and/or new or ongoing adverse events;
- 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).

The following evaluation will be performed on **Week 8 prior to EP (if following Table 6 only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 8 after IP administration (if following Table 6 only)**:

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

6.1.2.6 Week 10

Calculated from Week 8 if Week 8 is a dosing visit, the following evaluations will be performed at this visit for **Part 1 and Part 2 if Day 0/Week 8 dosing regimen is optimal**:

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.7 Week 12

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.8 Week 30

The following evaluations will be collected during the follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

6.1.2.9 Week 48

Part 1

The following evaluations will be performed at this visit (End of Study visit):

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

Part 2

The Week 48 visit will be the End of Study visit for participants receiving only two doses. The Week 48 visit will be the last dosing visit for participants receiving three doses. The following evaluations will be performed on **Week 48 (complete prior to IP administration for Part 2 participants receiving a third/booster dose)**:

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

- Targeted physical examination (Section 6.4) for Part 2 participants receiving a third/booster dose;
- Full physical examination (Section 6.4) for Part 2 participants receiving two doses only;
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4) for Part 2 participants receiving a third/booster dose;
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

The following evaluation will be performed on **Week 48 prior to EP (for Part 2 participants receiving a third/booster dose only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 48 after IP administration (for Part 2 participants receiving a third/booster dose only)**:

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

6.1.2.10 Week 50

The following evaluations will be performed at this visit **only for Part 2 participants receiving a third/booster dose:**

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.11 Week 68

The following evaluations will be performed at this visit (End of Study Visit) **only for Part 2 participants receiving a third/booster dose**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.2 INFORMED CONSENT

All participants 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 participants
- Explain the clinical trial
- Provide clinical trial participants 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 60 day screening window.

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).

Participants meeting eligibility criteria listed in the protocol will be randomized by a computer generated allocation schedule.

6.4 SAFETY EVALUATIONS

PHYSICAL EXAM AND TARGETED PHYSICAL ASSESSMENTS

A full physical examination will be conducted during Screening and at study discharge/End of Study visit (i.e., Week 48, Week 68 or any other study discontinuation visit). 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 oral temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at select visits during the study.

HEIGHT AND WEIGHT

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

12-LEAD ECG

A single 12-lead ECG will be performed at Screening for all participants to determine eligibility. ECG results obtained within 60 days of Day 0 are acceptable. The ECG should include measurements of ventricular rate, PR, QRS, QT, QTcb or QTcf, as well as an assessment of whether the ECG is normal or abnormal. Abnormal ECGs should be interpreted as clinically significant or not clinically significant. Dosing will be delayed in the event of a clinically significant abnormal pre-dose ECG until it has been reviewed by the PI, qualified PI designee, MM or Sponsor consultant cardiologist and deemed safe to proceed.

LABORATORY EVALUATIONS

At Screening and select visits during the study, blood samples will be collected for safety assessments. Approximately 400 mL and 340-460 mL of blood will be drawn from each subject in Part 1 and Part 2, respectively, over the course of the study. Participants may be asked to come back 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 select visits during the study.

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, BUN (blood urea nitrogen), and Creatinine (Cr) will be measured at Screening and select visits during the study.

Liver function:

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will be measured at Screening and select visits during the study.

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and select visits during the study. If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

Antibodies to MERS-CoV (per PI discretion), Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and HIV antibody or rapid test will be measured at Screening only.

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 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 participant is pregnant prior to completing the specified dose regimen, then no further IP will be administered. Every attempt should be made to follow pregnant participants for the remainder of the study and to determine the outcome of the pregnancy.

6.4.1 INJECTION AND EP

Participants in Part 1 Study Groups A, B and C will receive one injection of INO-4700 in a volume of ~0.1 mL by ID injection above an acceptable muscle location for injection, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups D and E will receive two injections of INO-4700, each in a volume of ~0.1 mL, above an acceptable muscle location on two different limbs, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups F and G will receive one injection of placebo in a volume of ~0.1 mL by ID injection above an acceptable muscle location for injection, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups H and I will receive two injections of placebo, each in a volume of ~0.1 mL, above an acceptable muscle location on two different limbs, the injection site is assessed for IP leakage, and the injection is followed immediately by EP.

Participants in Part 2 will receive one or two injections per dosing visit of the optimal dose of INO-4700 or placebo in volume of ~0.1 mL by ID injection above an acceptable skin location for injection, the injection site is assessed for IP leakage, and the injections is followed immediately by EP.

Only if the deltoid muscle is not a suitable location (see exclusion criterion ‘h’), 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, previous injection site at the same dosing visit, 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 ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

Participants may be offered topical anesthetic (e.g., EMLA or equivalent) to prevent discomfort from the injection/EP procedure. If a topical anesthetic is used, an approximate 1.5 cm diameter amount will be applied without occlusion to the administration site ~30 minutes prior to injection/EP.

Participants may be offered a mild sedative (e.g., 0.5-1 mg lorazepam or equivalent) for anxiety related to the injection/EP procedure. Mild sedatives may be administered approximately 1 hour prior to injection/EP on dosing visits. Participants who receive a mild sedative must not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

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

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

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, liver function, and hematology and urinalysis performed at the visits listed in the Schedule of Events (Tables 3, 4 and 5) 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).

6.4.4 ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AEs)

Participants 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. Participants 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 to 12 weeks from Day 0. Subsequently, only related adverse events, adverse events of special interest and serious adverse events will be collected until study discharge. 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 7 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 7: 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 to assess overall immune response. Immunology blood and serum samples are to be collected at Screening and select visits during the study. Both Screening and Day 0 immunology samples are required to enable all immunology testing. 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-4700 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.

An immune responder is defined as having either an increase in vaccine antibody titer compared to baseline or an increase in the number of vaccine specific IFN-gamma secreting cells as compared to baseline.

Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

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 the case report forms (CRFs).

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented.

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

Participants should refrain from becoming pregnant until 1 month following the last dose of investigational product by using appropriate contraceptive measures (see Section 4.1).

Participants must not be vaccinated (e.g., influenza vaccine) within 2 weeks prior to the first dose of INO-4700 or placebo, or within 2 weeks of (before or after) any subsequent dose of investigational product.

Participants must not receive a course of systemic corticosteroids (≥2 mg/kg of prednisone or equivalent for 5 days) within 3 months prior to any dose of investigational product.

Participants must not have fever (oral temperature >38.0 degrees Celsius or 100.4 degrees Fahrenheit) within 72 hours prior to each dose of investigational product.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4700 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 to have a causal relationship with this treatment.

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

Adverse Events (AEs) include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of clinical trial drug)
- Any pre-existing condition 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

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 participant 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 participant 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 participant'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 participant or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clarification of Serious Adverse Events (SAEs)

- Death in itself is not an AE. Death is an outcome of an AE, but when the cause of death has not been provided, use the event term: death of unknown cause.
- The participant 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 participants.

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 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.

7.8.3 CLINICAL TRIAL STOPPING RULES

The stopping rules for this study are any of the following:

- Any study treatment-related SAE.
- Any Grade 4 toxicities related to study treatment.

- Any report of anaphylaxis from study treatment.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained to 12 weeks from Day 0. Subsequently, only related adverse events, AESIs and serious adverse events will be collected until study discharge. This information will be captured in the Electronic Data Capture (EDC) system.

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

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

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 8: SAE Contact Information

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

Table 9: Medical Monitor Direct contact Information

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

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

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

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

- Redact the medical records of all personal data (e.g., confidential subject data, Personal Identifying Information [PII])
- Provide the 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 participants) 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 participant 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

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

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (Part 1 – Week 48 and Part 2 – Week 48 or Week 68) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after enrolling in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the PI and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

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

The clinical trial site must request the subject's permission to query pregnancy outcome and follow the subject for outcome of the pregnancy. The subject will continue to be followed for safety assessments without receiving additional IP until clinical trial discharge in accordance with this protocol. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. The PI should use clinical

judgment regarding subsequent clinical trial-related blood collection based on the presence or absence of anemia in each subject.

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

7.13 NOTIFYING REGULATORY AUTHORITIES AND INSTITUTIONAL REVIEW BOARDS (IRBS)/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 probably or possibly related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor. Additionally, if the trial is discontinued for any reason (Section 7.15), all enrolled subjects still participating in the study will undergo the end of study evaluation prior to discontinuation from the study and any reported SAE or AESI will be followed by the PI until resolution or return to baseline status, or stabilization of the reported event (i.e., the expectation that it will remain chronic).

7.15 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at this site or at multiple sites for safety or administrative reasons at any time. In particular, a clinical trial site that does not recruit at a reasonable rate may be discontinued. Additionally, the clinical trial may be discontinued at any time by an IRB/REB/EC, INOVIO, or a regulatory authority as part of their duties to ensure that clinical trial participants 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 documentation of the statistical and analytical plan is presented below.

8.2 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals, or its representative. This is a randomized across Study Group, investigator-and-participant blinded, placebo-controlled (SSC-0001), multi-center phase 2a trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered in healthy adult volunteers. Approximately 542 volunteers will be evaluated across two (2) parts: Part 1 Dose Finding and Part 2 Expansion.

Approximately 192 participants in Part 1 will be randomized across each group (A through I; see Table 1) to receive either INO-4700 or placebo. Upon completion of the Week 10 visit by all Part 1 participants including evaluable immunological data from all Study Groups, one optimal Study Group dose and regimen will be selected for expansion into Part 2. Participants in Part 1 will be followed until Week 48.

Approximately 350 participants in Part 2 will be randomized to receive the optimal dose of INO-4700 or placebo (see Table 2). The first 225 participants randomized in parallel to three Study Groups will receive a third dose of either INO-4700 or placebo at Week 48. Participants will either receive a week 48 active treatment administration on top of their two prior active treatment administrations (N=100), or a week 48 placebo administration on top of their two prior active treatment administrations (N=100) or a week 48 placebo administration on top of two prior placebo administrations (N=25). Collectively, these first 225 participants will be followed until Week 68. The remaining 125 participants will be randomized in parallel to either 2 active treatment administrations (N=100) or 2 placebo administrations (N=25) and followed until Week 48.

Details on the Study Group design and conduct and frequency of DMSB meetings can be found in Sections 3.0 and 12.1.

The trial's primary analyses pertains to the evaluation of the tolerability, safety and overall immune response to INO-4700 administered by ID injection followed by EP in healthy volunteers. Exploratory analyses concern the evaluation of the expanded immunological response to INO-4700 delivered by ID injection followed by EP.

8.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis will be tested in Part 1 of this trial. The hypothesis in Part 2 of this trial is H0: $p \leq 70\%$ versus H1: $p > 70\%$, where p denotes the true population overall immunological response rate for the selected optimal dose of INO-4700.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The modified intention to treat (mITT) population includes all participants who receive at least one dose of the INO-4700 or placebo. Participants in this sample will be analyzed by their original assigned dose of INO-4700 or placebo. The mITT population will be used to analyze co-primary and exploratory immunological endpoints.

The per-protocol (PP) population is comprised of mITT participants who receive all their planned administrations and who have no Medical Monitor-assessed important protocol violations. Analyses on the PP population will be considered supportive of the corresponding mITT analyses. Participants excluded from the PP population will be identified and documented prior to locking the study database.

The safety analysis population includes all participants who receive at least one dose of INO-4700 or placebo administered by ID injection. Participants for this population will be grouped in accordance with the dose of INO-4700 or placebo that they received. This population will be used for all safety analyses in the study.

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY SAFETY ANALYSES

The primary analyses for this trial are safety analyses of treatment emergent adverse events (TEAEs), administration site reactions and clinically significant changes in safety laboratory parameters from baseline.

TEAEs are defined for this trial as any AEs/AESIs/SAEs that occur on or after Day 0 following IP administration. All TEAEs will be summarized by frequency, percentage and associated 95% Clopper-Pearson confidence interval, and in Part 2, the difference in the percentage between those who received INO-4700 and their corresponding same

regimen placebo together with associated 95% confidence interval. Related SAEs and related Grade 3 or higher AEs will also be analyzed as described above within and between associated placebo in part 1. The frequencies will also be presented separately by dose number and will be depicted by system order class and preferred term. Additional frequencies will be presented with respect to maximum severity and relationship to IP. Multiple occurrences of the same AE in a single subject will be counted only once following a worst-case approach with respect to severity and relationship to IP. All serious TEAEs will also be summarized as above. AE duration will be calculated as AE stop date – AE start date + 1 day. AEs and SAEs that are not TEAEs or serious TEAEs will be presented in listings.

All of these primary safety analyses will be conducted on the participants in the safety population.

8.5.2 PRIMARY IMMUNOGENICITY ANALYSES

For both Part 1 and Part 2, antigen specific binding antibody titers, MERS-CoV neutralizing antibody titers, and specific cellular immune responses will be analyzed by Study Group. Binding antibody titer will be analyzed for each Study Group using the geometric mean and associated 95% confidence intervals. Percent neutralizing antibodies and antigen specific cellular immune response increases will be analyzed for each Study Group using medians, inter-quartile range and 95% confidence intervals. Percentage with overall immune response, inclusive of seroconversion (i.e., positive titer), and corresponding 95% Clopper-Pearson confidence intervals will be analyzed within each Study Group.

In Part 1, the difference in percentage of overall immune responders including seroconverters between all pairs of INO-4700 Study Groups will be calculated along with corresponding exact 95% confidence intervals.

In Part 2, the primary hypothesis of H0: $p \leq 70\%$ versus H1: $p > 70\%$ will be tested with an exact test of a binomial proportion. In addition, the binding antibody titer difference between INO-4700 and placebo will be analyzed using the geometric mean fold ratio and associated 95% confidence interval. Percent neutralizing antibodies and antigen specific cellular immune response differences between INO-4700 and placebo will be analyzed using the difference in medians and associated 95% confidence intervals.

All of these primary immunogenicity analyses will be conducted on the participants in the mITT and PP populations.

8.5.3 SAFETY ANALYSES

Laboratory response variables will be descriptively summarized in accordance with time point and as changes from baseline including 95% confidence intervals. Laboratory values considered clinically significant will be presented in listings for participants in the safety population.

Measurements for vital signs as well as changes from baseline will be descriptively summarized by time point for participants in the safety population.

Serum pregnancy at Screening and urine pregnancy at each post baseline time point will be descriptively summarized for participants in the safety population.

The percentage of participants with abnormal medical history findings will be summarized by body system and preferred term for participants in the safety and mITT populations.

For statistical analysis purposes, prior medications are defined as those that were used and stopped before the start of the trial (prior to Day 0) and concomitant medications are

defined as those used during the course of trial (on or after Day 0). Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages for participants in the safety and mITT populations.

8.5.4 DISPOSITION

Subject disposition will be summarized for all randomized participants and will include the number and percentage randomized, the number and percentage who received each planned dose and the number who completed each part of the trial. The number and percentage of participants who discontinued IP in each part of the trial 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

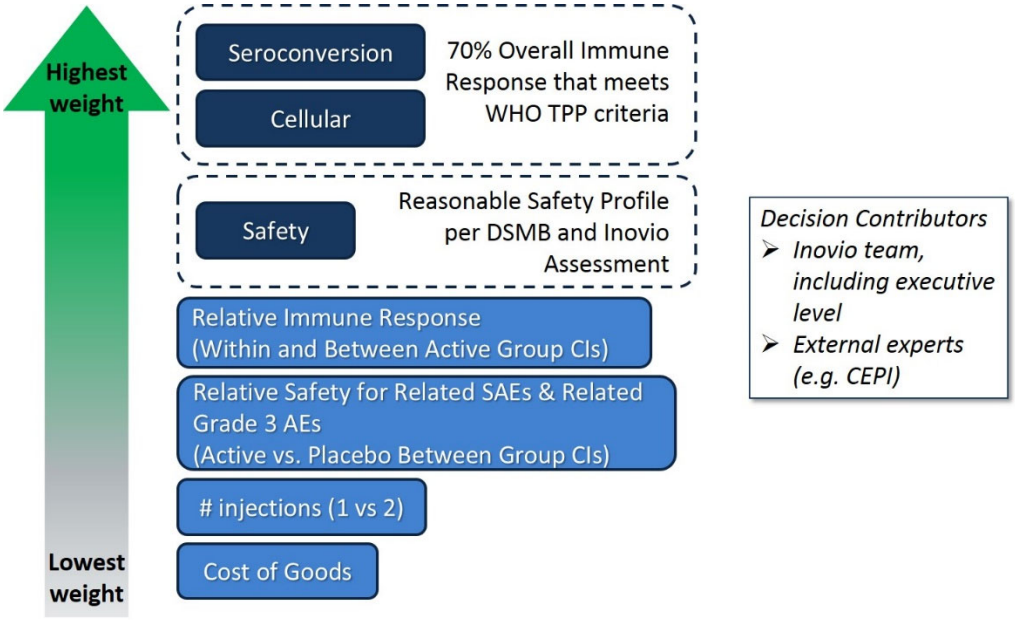
Demographic and baseline characteristic data will be descriptively summarized for participants in the safety and mITT populations.

8.5.6 INTERIM ANALYSES

No formal interim analyses will be performed for this trial. However, safety and tolerability will be assessed by the DSMB as noted above for the participants in each Study Group.

A Sponsor unblinded review of the week 10 immunogenicity and safety data will be made during Part 1 of this study when all evaluable data observations are available in order to determine the optimal dose for the Part 2 of the study. The selection of the optimal dose for Part 2 will involve consideration of weighted ordered criteria described in Figure 3 below.

Figure 3: Weighted Ordered Dose Selection Criteria



At a minimum, the optimal selected dose will have a 70% overall immune response and acceptable safety profile as determined by the DSMB and Inovio Medical Council. Other criteria listed in Figure 3 will contribute to the selection of the right optimal dose if the overall immune responses and safety profiles are similar between the Study Groups in Part 1.

A group-level unblinded review of the immunogenicity and safety data will be made once week 12 visit immunology data are complete for all participants in Part 2 whilst maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all participants with remaining visits through to the final visit. These summaries and analyses will allow the Sponsor and collaborators to have results with respect to the immunogenicity endpoints corresponding to the Part 2 Week 12 visit on which to inform product development goals. 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. Thus, Part 2 of the trial will remain blinded to the Sponsor and collaborators with respect to subject treatment assignment.

8.5.7 MULTIPLICITY

No adjustment for multiplicity will be made for this trial.

8.5.8 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

8.5.9 EXPLORATORY ANALYSES

T and B post baseline cell number will be analyzed descriptively by Study Group using the mean or median and associated 95% confidence intervals.

In Part 2, treatment difference comparisons will include a comparison of two dose INO-4700 participants who are boosted with INO-4700 versus two dose INO-4700 participants who are boosted with placebo.

Exploratory ANCOVA and Logistic models may be fit that include baseline, confounder variables such as age and gender to test the relationship between study group and different immune response variables.

8.6 SAMPLE SIZE/POWER

No formal power analysis is applicable to Part 1 of this trial, as descriptive statistics will be used to summarize the data.

For each Study Group in Part 1 of the trial with 32 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <11% if no SAEs are observed in a study group. For all the Study Groups combined in Part 1 of the trial with 160 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <3% if no SAEs are observed in this study phase. For all Study Groups combined across Parts 1 & 2 of the trial with 460 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <1% if no SAEs are observed.

For Part 2 of this trial, an evaluable sample of 260 active subjects treated with INO-4700, which will be used for formal hypothesis testing, provides >90% power to detect an INO-4700 overall immunological response rate of 70% or higher should this overall response rate truly be 80%, using a one-sided type 1 error rate of 0.025.

8.7 RANDOMIZATION AND BLINDING

Part 1 of this study will be randomized across Study Groups (A through I). Part 2 of this study will be randomized between the selected optimal Active dose from Part 1 and placebo groups. The study is Investigator-and-participant blinded except for the site

pharmacy across all Study Groups for both parts of the study. The Sponsor will be blinded in Part 1 until Week 10 and blinded for the entire duration of Part 2 of the study.

For the Part 2 Week 12 analysis, group level unblinded summaries of immunogenicity and safety will be produced. The Sponsor will continue to remain blinded to subject-level treatment allocation for the remainder of the trial.

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 participant 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), if applicable

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 PARTICIPANTS

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

Participants are not required to follow special instructions specific to the IP used in this clinical trial. Participants will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should 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 participants, 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 participants 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. Participants must not be identified by name on any CRFs. Participants 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 Medical Monitor will regularly review safety and tolerability data throughout the trial in a blinded fashion until unblinding. Additional safety reviews will be conducted by a DSMB, and they will be responsible for reviewing all unblinded safety data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data. Safety reviews will include data from all enrolled participants.

The DSMB is not blinded to IP allocation and will review unblinded safety data. The DSMB will be charged with advising whether there appears to be any safety concerns and to make recommendations regarding continued enrollment, trial pause and trial suspension. If the safety data is considered unsatisfactory during any safety review, the study may be paused or stopped. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants. For further details see 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. Records for all clinical trial participants in this clinical trial will be monitored. The following clinical trial site monitoring tasks will be performed at all clinical trial sites:

- Prior to subject screening at the site, a Site Initiation Visit will be conducted to review all relevant forms and documentation, and ensure that the clinical trial site staff are qualified and compliant with all applicable requirements
- All clinical trial site monitoring visits will be documented
- Periodic clinical trial site visits will be performed throughout the clinical trial
- The blinded 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities 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 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.

- The unblinded 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 while maintaining the blind and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor while maintaining the blind.
  - Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
  - Assure that the pharmacy continues to be acceptable.
  - Assure that investigational drug accountability and reconciliation of records are complete and accurate.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and is fully supporting the study with funding provided by the Coalition for Epidemic Preparedness Innovations (CEPI). 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, ICH E6 and/or local regulations, where applicable.

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	Attributable, Legible, Contemporaneous, Original, and Accurate
bGH polyA	Bovine growth hormone 3' end poly-adenylation signal
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CEPI	Coalition for Epidemic Preparedness Innovations
Cl	Chloride
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electroporation
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
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
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
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

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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 MERS-CoV vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalopathy
	Encephalitis
	Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
	Enhanced disease following immunization
Other	Local/systemic SAEs (regulatory criteria)
	Acute renal failure
	Death, including maternal death, spontaneous abortion, stillbirth and neonatal death

Signature Page for VV-TMF-00167 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 30-Mar-2020 21:00:58 GMT+0000

Signature Page for VV-TMF-00167 v1.0

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Sponsored by:
Inovio Pharmaceuticals, Inc.

Protocol Version: 2.0

Protocol Version Date: 12Feb2021

Medical Monitor Approval Page

Drug: INO-4700

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], MD
[redacted]
Inovio Pharmaceuticals, Inc.

Date (ddMmmyyyy)

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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 protocol changes from v1.0 23Mar2020 to v2.0 12FEB2021. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Exclusion Criteria and Restrictions related to receipt of other vaccinations have been updated due to anticipated availability of the COVID-19 vaccine. Previously, participants were not to receive other vaccinations within 2 weeks before or after dosing. This has been amended to prohibit receipt of other vaccinations from 30 days prior to Day 0 until completion of the study visit occurring 2 weeks after the second dose of investigational product (i.e. the Week 6 visit if dosed at Week 4 and the Week 10 visit if dosed at Week 8). For Part 2B, receipt of other vaccinations is also prohibited from 2 weeks prior to the Week 48 visit through the Week 50 visit.
2. Exclusion criteria has been updated to no longer prohibit prior receipt of an investigational vaccine product for SARS.
3. The collection of adverse events has been updated so that all adverse events will be collected throughout the study, rather than only collecting related adverse events, adverse events of special interest and serious adverse events subsequent to the Week 12 visit. This will allow for improved safety assessment after the Part 2, Week 48 booster dose.
4. The timeline for contraception requirements has been updated so that contraception must be used from screening until 3 months following last dose, rather than from screening to 1 month following last dose, for consistency across the Sponsor's infectious disease programs. Exclusion criteria a was also updated accordingly.
5. At the Principal Investigator's discretion, collection of the screening immunology samples may be postponed and collected along with the Day 0 samples. This may decrease the unnecessary collection of immunology samples from participants that fail screening.
6. The following changes have been made to the visit procedures:
    a. Week 2, Part 1 and Part 2: Collection of immunology samples has been removed. Based on experience across DNA vaccine studies, the week 2 sample is not needed to adequately assess immune response.
    b. Week 12, Part 1 and Part 2 (Day 0 & Week 8): Collection of immunology samples has been removed. Based on experience across DNA vaccine studies, the week 2 sample is not needed to adequately assess immune response. These visits have been updated to follow-up phone calls for collection of adverse events.
    c. Week 8, Part 2 (Day 0 & Week 8): Collection of immunology samples has been added. This will allow for better assessment of immune response after one dose.
7. Applicable footnotes for Tables 4, 5 and 6 have been updated to reflect whole blood collection in 4 x 8.0 mL (32 mL) Cell Preparation Tubes (CPT) rather than 4 x 8.5 mL (34 mL) Acid Citrate Dextrose (ACD) tubes. A total of 64 mL will be collected prior to first dose, rather than 68 mL.
8. The Exploratory Objectives, Exploratory Endpoints and Statistical Analysis Plan have been updated to include evaluation of humoral immune response of MERS-CoV spike protein and cross reactivity to other coronavirus spike proteins.
9. Total blood collection volume has been updated to reflect current standard volumes and the switch from ACD to CPT tubes.
10. A statement clarifying that participants who discontinue or withdraw from the study will not be replaced, has been added.
11. Examples of the Investigational Product vial and carton labels have been added.
12. The SAE reporting contact information has been updated.
13. The Medical Monitor contact information has been updated.

14. A statement indicating investigators will request follow-up from pregnant participants or pregnant partners 30 days after the end of pregnancy, has been added.
15. COVID-19 was added as an Adverse Event of Special Interest.
16. Statements clarifying that all pregnancy and safety information will be entered into the Sponsor's safety database have been added.
17. A statement that eSource will be utilized in this study has been added.
18. A statement was added to Section 8.4.6 to clarify how the blind will be protected if the number of subjects who experience an event is greater than 0 and the count of these events relative to the total count of events produces a percentage less than 3% for a given analysis.
19. Section 7.8.1.1 was added to clarify management of COVID-19 infection and vaccination.
20. It was clarified that bicarbonate results can be HCO_3 or CO_2.
21. It was clarified that SSC-0001 may be packaged at a volume of 1.1 mL in 2 mL vials, in addition to 2.0 mL in 10 mL vials, as any future lots of SSC-0001 may be packaged as such.

Table of Contents

CLINICAL PROTOCOL SYNOPSIS

Protocol Title: Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Number: MERS-201

Clinical Trial Phase: 2a

Estimated Number of Clinical Trial Centers and Countries/Regions: Approximately nine (9) to ten (10) centers in the Middle East and Africa Regions. Additional sites and countries may be added as necessary.

Clinical Trial Design:

This is a Phase 2a, randomized, blinded, placebo-controlled, multi-center trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered by intradermal (ID) injection followed by electroporation (EP) using the CELLECTRA™ 2000 device in healthy adult volunteers. The primary objectives of this trial are to evaluate the tolerability, safety and immunogenicity of INO-4700 administered by ID injection followed by EP in healthy adult volunteers according to the regimens outlined in Table 1, Table 2, Table 3 and Figure 1.

Approximately 542 healthy volunteers will be evaluated across two (2) parts of this study, Part 1 and Part 2. INO-4700 or placebo (SSC-0001) will be administered ID in ~0.1 mL dose volume followed immediately by EP.

Part 1 – Dose Finding

In Part 1, approximately 192 participants ages 18-50 years will be assessed through five (5) dose levels and regimens. These five (5) dose levels and regimens will be evaluated across nine (9) groups designated Study Groups A, B, C, D, E, F, G, H and I. Study Groups A, B, C, D and E will receive INO-4700 and enroll approximately 32 participants per group. Study Groups F, G, H and I will receive placebo and enroll approximately 8 participants per group.

Table 1: MERS-201 Part 1 Dose Groups

	Study Group	Number of Participants	Dosing Weeks	Number of Injections + EP per Dosing Visit	INO-4700 (mg) per injection	Total Dose of INO-4700 (mg)
Active	A	32	0, 4	1	0.6	1.2
	B	32	0, 4	1	1.0	2.0
	C	32	0, 8	1	1.0	2.0
	D	32	0, 8	2[a]	0.5 + 0.5 (1.0)	2.0
	E	32	0, 4	2[a]	1.0 + 1.0 (2.0)	4.0
Total Active		**160**				
Placebo	F	8	0, 4	1	—	—
	G	8	0, 8	1	—	—
	H	8	0, 8	2[a]	—	—
	I	8	0, 4	2[a]	—	—
Total Placebo		**32**				
Total		**192**				

[a]INO-4700 will be injected ID followed by EP in an acceptable location on two different limbs at each dosing visit

Participants will be randomized to receive either INO-4700 or placebo according to the dosing schedule described in Table 1. All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo) within each Study Group, with the exception of the site's pharmacy personnel.

Enrollment into all Study Groups will proceed in parallel. After the first four (4) participants in Active Study Groups and the first two (2) participants in Placebo Study Groups have Week 2 clinical laboratory and adverse event data available, the results will be reviewed by the Data Safety and Monitoring Board (DSMB) (Figure 1). Enrollment will not be paused during this DSMB review, and screening and randomization may continue.

Upon completion of the Week 10 visit and availability of immunological data, Part 1 will be unblinded in order to allow for one regimen to be selected for advancement into Part 2. The Study Group with an optimal immune response, an acceptable safety profile and tolerant dosing regimen by Week 10, will be selected for Part 2. The Sponsor will remain blinded through Part 1 of the study until initiation of the Week 10 data review.

All Part 1 participants will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

Part 2 – Expansion

In Part 2, approximately 350 participants will be evaluated across one (1) dose level and regimen as outlined in Table 2 and Table 3. The dose level and regimen will be identified based on the optimal dose selection from Part 1. Enrollment into Part 2 may begin following completion of the Week 10 optimal dose and regimen selection in Part 1 (i.e., prior to Week 48 completion in Part 1).

Table 2: MERS-201 Part 2A Dose Groups

Study Group	Number of Participants	Dosing Weeks	Dose and Regimen
Active	300	0, 4 or 8	TBD
Placebo	50	0, 4 or 8	TBD
Total	**350**		

Table 3: MERS-201 Part 2B Dose Groups

Study Group	Number of Participants	Dosing Week	Dose and Regimen
Active – Booster	100[a]	48	TBD
Active – Placebo	100[b]	48	TBD
Placebo	25[c]	48	TBD
Total	**225**		

[a]First (Day 0), second (Week 4 or 8) and third (Week 48 booster) doses will be INO-4700.
[b]First (Day 0) and second (Week 4 or 8) doses will be INO-4700. Third dose will be a placebo dose at Week 48.
[c]Placebos will also receive a third dose in order to maintain blinded design. First (Day 0), second (Week 4 or 8) and third (Week 48) doses will be a placebo dose.
TBD, to be determined based on Part 1 optimal dose and regimen selection

In Part 2A, participants will be randomized to receive the optimal dose of active (INO-4700) selected in Part 1 of this study or placebo (SSC-0001) (Figure 1). Approximately 300 participants will receive INO-4700 and 50 participants will receive placebo.

In Part 2B, the first 200 participants randomized to the Part 2A Active Study Group will receive a third dose of either INO-4700 or placebo at Week 48. Specifically, Study Group "Active – Booster" will receive INO-4700 at the first (Day 0), second (Week 4 or 8) and third (booster at Week 48) doses. Study Group "Active – Placebo" will receive INO-4700 at the first (Day 0) and

second (Week 4 or 8) doses, and placebo at the third (Week 48) dose. Similarly, in Part 2B, the first 25 participants randomized to the Part 2A Placebo Study Group will receive a third dose of placebo at Week 48. Collectively, these first 225 participants will be followed for 68 weeks from the Day 0 dosing [i.e., Week 68 will be the planned End of Study (EOS) visit]. All remaining 125 participants in Part 2A (i.e., those receiving only 2 doses) will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo), with the exception of the site's pharmacy personnel. Enrollment into Active and Placebo Study Groups will proceed in parallel. No enrollment pauses are planned.

Upon completion of the Week 12 visit and availability of immunological and safety data, group-level (INO-4700 or placebo) unblinded summaries of immunogenicity and safety will be produced. This Week 12 analysis will serve to inform product development goals. The Sponsor will continue to remain blinded to subject-level treatment allocation (i.e., INO-4700 or placebo) for the remainder of the trial.

DSMB for Parts 1 and 2

The DSMB will remain unblinded throughout the duration of the study.

In Part 1, the DSMB will review clinical laboratory and adverse event data for the first six (6) participants, 4 active and 2 placebos, in each Active and Placebo Study Group, respectively, after the Week 2 safety data are complete. The DSMB will again convene to review all available safety data for all Study Groups after approximately 50% of planned participants are enrolled (i.e., approximately 96 participants), and once enrollment is complete.

Subsequently, the DSMB will convene approximately every three (3) calendar months thereafter until study completion. Enrollment pauses are not planned during any DSMB review in Part 1 nor 2.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

Criteria for Evaluation:

Research Hypothesis:

- A selected optimal dose of INO-4700 delivered ID followed by EP using CELLECTRA™ 2000 in healthy volunteers will be well tolerated, exhibit an acceptable safety profile and result in generation of immune responses to MERS-CoV.

Primary Objectives:

- Evaluate the tolerability and safety of INO-4700 administered by ID injection followed by EP in healthy adult volunteers
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for identification and confirmation of an optimal dose and regimen
- Evaluate selected optimal dose for safety and immunogenicity

Primary Safety Endpoints:

- Incidence of adverse events by system organ class (SOC), preferred term (PT), severity and relationship to investigational product
- Administration (i.e., injection) site reactions (described by frequency and severity)
- Incidence of adverse events of special interest

Primary Immunogenicity Endpoints:

- Overall immune response
  - MERS-CoV antigen specific antibodies
  - Antigen specific cytokine-producing T cell responses

Exploratory Objective:

- Evaluate the expanded immunological profile by assessing both T and B cell immune responses
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for impact of boosting with a third dose
- Evaluate humoral immune response cross reactivity to other coronaviruses

Exploratory Endpoint:

- Expanded immunological profile which may include (but not limited to) additional assessment of T and B cell numbers and T and B cell molecular changes by measuring immunologic proteins and mRNA levels of genes of interest at all weeks as determined by sample availability
- Antibodies to other coronaviruses

Safety Assessment:

For Part 1, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6, Week 10 and Week 48. For Part 2, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details.

For both Parts 1 and 2, all adverse events, regardless of relationship, will be collected from the time of consent until study discharge.

Additionally, for both Parts 1 and 2, a pregnancy test will be performed at screening and prior to each dose.

Immunogenicity Assessment:

For Part 1, immunology blood samples will be collected at Screening, Day 0, Week 6, Week 10 and Week 48. For Part 2, immunology blood samples will be collected at Screening, Day 0, Week 6 (if optimal regimen includes dosing at Week 4), Week 8 (if optimal regimen includes dosing at Week 8), Week 10 (if optimal regimen includes dosing at Week 8), Week 12 (if optimal regimen includes dosing at Week 4), Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details. Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

Clinical Trial Population:

Part 1 – Healthy adult volunteers between the ages of 18-50 years, inclusive.

Part 2 – Healthy adult volunteers at least 18 years of age.

Inclusion Criteria:

a. Able to provide informed consent and have signed Informed Consent Form (ICF) prior to screening procedures;
b. For Part 1, adults age 18 and 50 years, inclusive. For Part 2, adults at least 18 years of age;
c. Judged to be healthy by the Investigator on the basis of medical history, physical examination and vital signs performed at Screening; **Note:** Participants taking daily prescription or non-prescription medications for management of acceptable chronic medical conditions must be on a stable dose, as defined by non-change in dose for the 3 months prior to the first dose of study medication and no planned changes during the active dosing period of the study;
d. Able and willing to comply with all study procedures;
e. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
f. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening;
g. Screening ECG deemed by the Investigator as having no clinically significant findings (e.g. Wolff-Parkinson-White syndrome);
h. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or have a partner who is sterile (i.e., vasectomy in males at least six (6) months prior to enrollment or tubal ligation, absence of ovaries and/or uterus in females);
    - 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. Pregnant or breastfeeding, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit until 3 months following last dose;
b. Positive serum pregnancy test during screening or positive urine pregnancy test prior to dosing;
c. History of respiratory diseases such as asthma, chronic obstructive pulmonary disease or chronic bronchitis;
d. Is currently participating in or has participated in a study with an investigational product within 30 days preceding Day 0;
e. Previous receipt of any vaccine within 30 days preceding Day 0 or planning to receive any vaccine during the timeframe restricted per the protocol;
f. Previous receipt of an investigational vaccine product for prevention of MERS;

g. Prior exposure to MERS-CoV or camels (serology or antibody testing will be requested at the Investigator's discretion);
h. Participants who participated in MERS-201 Part 1 cannot participate in MERS-201 Part 2;
i. Fewer than two acceptable sites available for ID injection and EP considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site;
    b. 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);
    c. Any metal implants or implantable medical device within the electroporation site;
j. Prisoner or participants who are compulsorily detained (involuntary incarceration);
k. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids) prior to dosing. Systemic corticosteroids must be discontinued at least 3 months prior to first dose;
l. Reported active drug or alcohol or substance abuse or dependence.

Clinical Trial Treatment:

- Part 1 Group A – One 0.6 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group B – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group C – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group D – Two 0.5 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group E – Two 1.0 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group F – One ID injection of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group G – One ID injection of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group H – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group I – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 2 – Dose and regimen to be determined, each ID injection(s) followed by EP administered at Day 0, Week 4 or Week 8, and Week 48 (for Part 2B participants receiving a third dose)

INO-4700 or placebo will be administered intradermally in ~0.1 mL dose volume followed immediately by EP.

Formulation:

INO-4700 in sodium chloride and sodium citrate, refrigerated. Placebo [sterile saline sodium citrate buffer (SSC-0001)], refrigerated.

FIGURE 1 – STUDY DESIGN AND DOSING SCHEMA

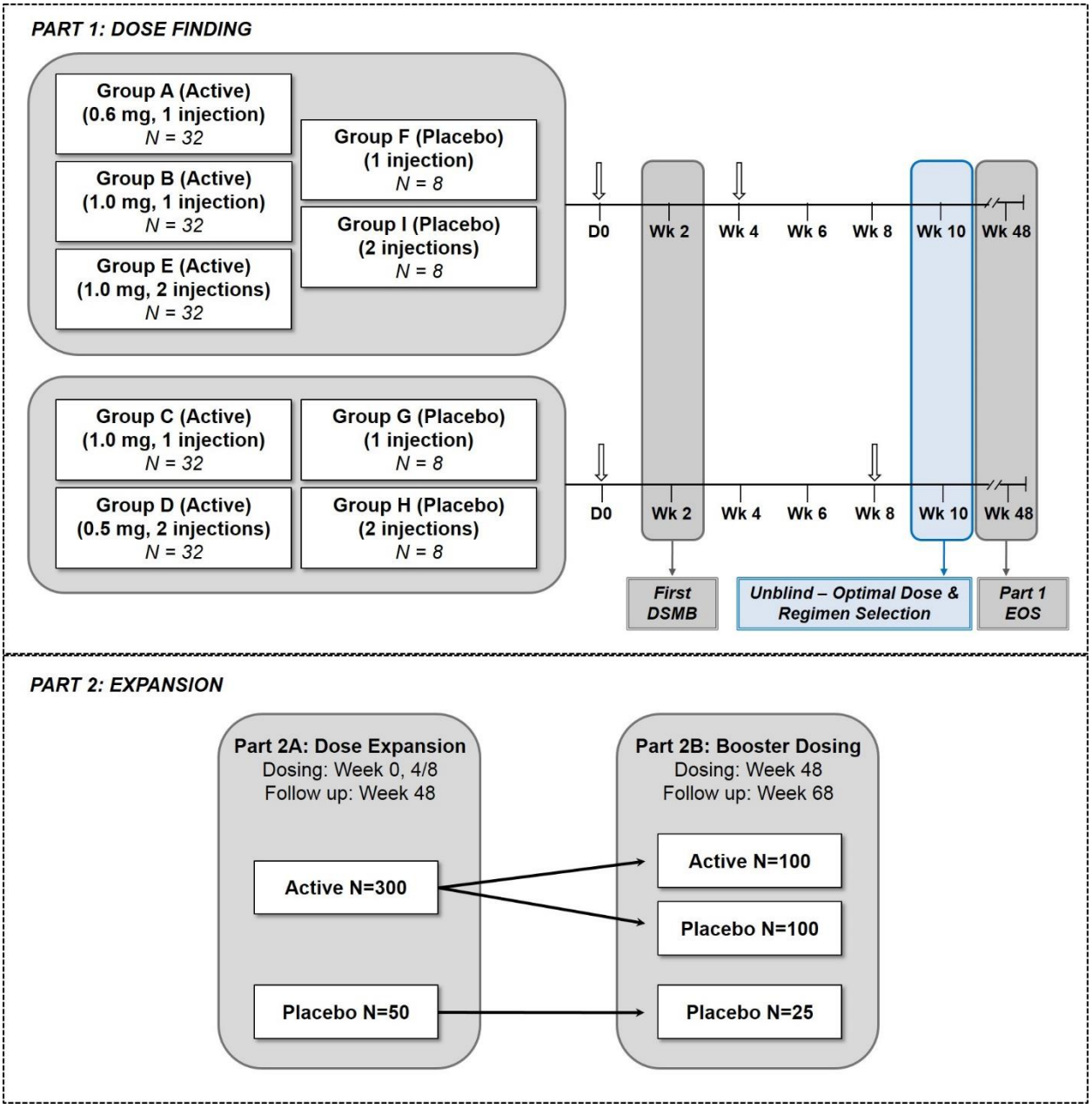


TABLE 4 – PART 1 TRIAL SCHEDULE OF EVENTS

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4 (± 5d)		Week 6 (± 5d)	Week 8 (± 5d)		Week 10 (± 5d)	Week 12[b] (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)
		Pre	Post		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
Physical Exam[c]	X	X		X	X		X	X		X			X
Vital Signs	X	X		X	X		X	X		X			X
Height and Weight	X												
CBC with Differential	X			X			X			X			X
Chemistry and Liver Function[d]	X			X			X			X			X
Serology[e]	X												
12-lead ECG	X												
Urinalysis Routine[f]	X			X			X			X			X
Pregnancy Test[g]	X	X			X[k]			X[l]					
INO-4700 or placebo + EP[h]		X[i,j]			X[i,k]			X[j,l]					
Download EP Data[m]			X			X[k]			X[l]				
Adverse Events[n]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology (Whole blood)[o]	X	X					X			X			X
Immunology (Serum)[p]	X	X					X			X			X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs
c. Full physical examination at screening and Week 48 (or any other study discontinuation visit) only. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3 or CO_2, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. For Study Groups A, B and F, one injection preferably over deltiod muscle at Day 0 and Week 4. For Study Groups E and I, two injections with each injection over a different deltoid or lateral quadriceps, preferably over the deltoid muscles, at Day 0 and Week 4.
j. For Study Groups C and G, one injection preferably over deltoid muscle at Day 0 and Week 8. For Study Groups D and H, two injections with each injection over a different deltoid or lateral quadriceps, preferably over the deltoid muscles, at Day 0 and Week 8.
k. Complete only for Study Groups A, B, E, F and I.
l. Complete for Study Groups C, D, G and H.
m. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
n. Includes AEs from the time of consent and all injection site reactions that qualify as an AE.
o. 4 x 8.0 mL (32 mL) whole blood in Cell Preparation Tubes (CPT) per time point. Note: At the investigator's discretion, rather than collecting a sample at screening, 64 mL (8 x 8.0 mL whole blood in CPT tubes) may be collected prior to dosing on Day 0.
p. 1 x 8 mL blood in 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. At the investigator's discretion, rather than collecting a sample at screening, 2 x 8 mL blood in two (2) 10 mL red top serum collection tubes (for eight aliquots of 1 mL each) may be collected prior to dosing on Day 0.

TABLE 5 – PART 2 TRIAL SCHEDULE OF EVENTS (DAY 0 & WEEK 4 OPTIMAL REGIMEN)

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4 (± 5d)		Week 6 (± 5d)	Week 8[b] (± 5d)	Week 12 (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)		Week 50[i] (± 5d)	Week 68[i] (± 10d)
		Pre	Post		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
Physical Exam[c]	X	X		X	X		X				X		X	X
Vital Signs	X	X		X	X		X				X		X	X
Height and Weight	X													
CBC with differential	X			X			X				X		X	X
Chemistry and Liver Function[d]	X			X			X				X		X	X
Serology[e]	X													
12-lead ECG	X													
Urinalysis Routine[f]	X			X			X				X		X	X
Pregnancy Test[g]	X	X			X						X[i]			
INO-4700 or placebo + EP[h]		X			X						X[i]			
Download EP Data[j]			X			X						X[i]		
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X
Immunology (Whole blood)[l]	X	X					X		X		X		X	X
Immunology (Serum)[m]	X	X					X		X		X		X	X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs.
c. Full physical examination at screening and Week 48 (participants receiving only two doses) or Week 68 (participants receiving three doses), as well as any other study discontinuation visit. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3 or CO_2, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test prior to dosing at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. Complete only for participants receiving a third dose of either INO-4700 or placebo (Part 2B).
j. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
k. Includes AEs from the time of consent and all injection site reactions that qualify as an AE.
l. 4 x 8.0 mL (32 mL) whole blood Cell Preparation Tubes (CPT) per time point. Note: At the investigator's discretion, rather than collecting a sample at screening, 64 mL (8 x 8.0 mL whole blood in CPT tubes) may be collected prior to dosing on Day 0.
m. 1 x 8 mL blood in 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. At the investigator's discretion, rather than collecting a sample at screening, 2 x 8 mL blood in two (2) 10 mL red top serum collection tubes (for eight aliquots of 1 mL each) may be collected prior to dosing on Day 0.

TABLE 6 – PART 2 TRIAL SCHEDULE OF EVENTS (DAY 0 & WEEK 8 OPTIMAL REGIMEN)

Tests and assessments	Screen[a]	Day 0		Week 2 (± 3d)	Week 4[b] (± 5d)	Week 8 (± 5d)		Week 10 (± 5d)	Week 12[b] (± 5d)	Week 30[b] (± 10d)	Week 48 (± 5d)		Week 50[i] (± 5d)	Week 68[i] (± 10d)
		Pre	Post			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
Physical Exam[c]	X	X		X		X		X			X		X	X
Vital Signs	X	X		X		X		X			X		X	X
Height and Weight	X													
CBC with differential	X			X				X			X		X	X
Chemistry and Liver Function[d]	X			X				X			X		X	X
Serology[e]	X													
12-lead ECG	X													
Urinalysis Routine[f]	X			X				X			X		X	X
Pregnancy Test[g]	X	X				X					X[i]			
INO-4700 or placebo + EP[h]		X				X					X[i]			
Download EP Data[j]			X				X					X[i]		
Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X
Immunology (Whole blood)[l]	X	X				X		X			X		X	X
Immunology (Serum)[m]	X	X				X		X			X		X	X

a. Screening assessment occurs from -60 days to -1 day prior to Day 0. If screening occurs within 14 days prior to Day 0, then do not repeat medical history prior to dosing.
b. Follow-up phone call to collect AEs.
c. Full physical examination at screening and Week 48 (participants receiving only two doses) or Week 68 (participants receiving three doses), as well as any other study discontinuation visit. Targeted physical exam at all other visits.
d. Includes Na, K, Cl, HCO_3 or CO_2, Ca, PO_4, glucose, BUN, Cr, AST and ALT.
e. MERS-CoV antibody (per PI discretion), HIV antibody or rapid test, HBsAg, HCV antibody.
f. Dipstick for glucose, protein, and hematuria. Microscopic examination should be performed if dipstick is abnormal.
g. Serum pregnancy test at screening. Urine pregnancy test prior to dosing at other visits.
h. INO-4700 or placebo is prepared by unblinded pharmacy personnel. All doses delivered via ID injection followed by EP.
i. Complete only for participants receiving a third dose of either INO-4700 or placebo (Part 2B).
j. Following administration of INO-4700 or placebo, EP data will be downloaded from the CELLECTRA™ 2000 device and provided to Inovio.
k. Includes AEs from the time of consent and all injection site reactions that qualify as an AE.
l. 4 x 8.0 mL (32 mL) whole blood in Cell Preparation Tubes (CPT) per time point. Note: At the investigator's discretion, rather than collecting a sample at screening, 64 mL (8 x 8.0 mL whole blood in CPT tubes) may be collected prior to dosing on Day 0.
m. 1 x 8 mL blood in 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. At the investigator's discretion, rather than collecting a sample at screening, 2 x 8 mL blood in two (2) 10 mL red top serum collection tubes (for eight aliquots of 1 mL each) may be collected prior to dosing on Day 0.

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 indicates that MERS-CoV infection remains a serious unmet medical need. Due to cross-species infection, both human and animal outbreaks are possible. Appropriate measures to prevent, control and treat existing and future infections are needed.

1.2 BACKGROUND INFORMATION

First reported in 2012 in a patient from Saudi Arabia presenting with pneumonia and acute kidney injury, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was originally known as coronavirus-EMS (Erasmus Medical Center) [1]. Although only more recently has human infection been identified, evidence suggests that MERS-CoV has existed in central and east Africa for decades [2]. MERS-CoV belongs to the family *Coronaviridae*, which includes four major groups: alpha, beta, gamma and delta. Although genomically related to the subgroup B beta-coronavirus severe acute respiratory syndrome (SARS) virus, MERS-CoV belongs to the subgroup C beta-coronavirus lineage. Two main recognized clades (clade A and B) of MERS-CoV have been identified by phylogenetic analysis, of which clade B can be further subdivided into five groups (groups I, II, III, IV, V). As a novel beta-coronavirus with high pathogenicity, significant morbidity and mortality is associated with infection of this subgroup, in contrast to less severe illness with other coronavirus infection [3].

Based on analyses of MERS-CoV's evolutionary history, natural hosts include bats *(species Neoromicia capensis* and *Vespertilio superans*), dromedary camel (*Camelus dromedarius*) and European hedgehog (*Erinaceus europaeus)* [4-7]. Its high recombination potential and evasion of host immune responses provides coronaviruses the ability to infect multiple host species, thus supporting the contribution of zoonotic events to adaptive evolution and disease transmission. Notably, dromedary camels are the only documented cross-species source for human infection [8]. However, the mechanism by which transmission occurs from natural animal hosts to human is still poorly characterized [9].

Those in a healthcare setting or who have come into contact with camels constitute the majority of known exposure routes and potential source of transmission [10]. Indeed, nosocomial transmission due to inadequate infection control has been established as a major driver of MERS-CoV infections in humans [11, 12], and contributed to the 2014 outbreak in Saudi Arabia and 2015 outbreak in South Korea. Primary cases tend to be middle-aged males and those with occupational exposure to animal hosts, while secondary cases include younger men and women and those who've come into contact with confirmed patients.

1.2.1 CLINICAL PRESENTATION AND IMMUNE RESPONSE

The incubation period for MERS-CoV is about 5-7 days and can be up to 12 days. MERS-CoV infection causes lower respiratory tract disease due to the highly susceptible nature of respiratory epithelial cells [13]. As such, greater viral loads are detected in the lower respiratory tract compared to the upper tract. Renal, intestinal and liver cells and

histiocytes can also be affected. Most common symptoms include fever, cough, shortness of breath and pneumonia, but myalgia, diarrhea, vomiting, chills and malaise have also been observed [10, 14]. Severe infection has been associated with acute kidney damage and respiratory distress requiring intensive care unit management within 2 days of hospital admission and can progress to multiorgan system failure [15]. Symptomatic patients carry MERS-CoV in tracheal aspirates, sputum and bronchoalveolar lavage fluid, and due to continuous viral shedding up to six weeks, patients may be able to transmit virus even when asymptomatic [16]. Poorer disease outcome and higher mortality may occur in older or immunocompromised patients and those with comorbidities, such as diabetes, cancer, and cardiac and chronic pulmonary disease [17].

Multiple studies suggest that host immune function and kinetics are important factors in determining disease course. Although higher antibody titers in correlation with greater viral load and delayed development of neutralizing antibodies were associated with poorer prognosis, the protective effect of these antibodies during infection is not clear [18, 19]. Additionally, both duration and magnitude of antibody response is indicative of disease severity [20]. From a cellular immunity perspective, MERS-CoV may downregulate expression of interferon-stimulated genes and delay induction of proinflammatory cytokines. Cytotoxic T cells are implicated in host defense and recovery as one study reported $CD8^+$ T cell responses in survivors despite the lack of an antibody response [18].

1.2.2 Current Treatment and Unmet Need

Current treatment focuses on symptomatic supportive care. Ribavirin and IFN-α2b administration have been shown to decrease viral replication *in vitro*, improve outcomes in animals and increase short-term survival in a retrospective human study [21, 22]. Ribavirin and IFN-α2b in combination with lopinavir is currently being tested in an interventional Phase 2 clinical trial (clinicaltrials.gov NCT02845843).

Other targets in development include viral and host proteases and viral entry inhibitors, such as inhibition of dipeptidyl-peptidase 4 (DPP4 or CD26) on the host cell. DPP4 acts as the main route of entry utilized by the virus' spike (S) protein, which is the primary target for neutralizing antibodies. Specifically, two monoclonal antibodies (REGN3051 and REGN3048) are able to bind the receptor binding domain (RBD) region within the S protein with high affinity and neutralize MERS-CoV *in vitro* [23]. In mouse models, these antibodies act as inhibitors against the DPP4 and S protein interaction and have shown effectiveness in restricting MERS-CoV replication and infection [23, 24]. Additional monoclonal antibodies, all targeting RBD, are being developed by several groups [25].

Importantly, vaccines have been prioritized as a promising alternative. Currently, there are no approved prophylactic nor therapeutic vaccines available for the prevention and treatment of MERS-CoV infection. Vaccine development for MERS-CoV may be challenging due to the sporadic nature of infection and lack of suitable animal models for challenge studies. Additionally, determinants of protection and immunity are not clearly defined. Development of both viral vector-based and RBD-based formats are ongoing. Replication deficient modified vaccinia Ankara (MVA) expressing full-length MERS-CoV spike protein and adenovirus vectors have demonstrated humoral and cellular immune responses, but adverse inflammation and safety remain a concern [26]. A live-attenuated MERS-CoV vaccine also exists but would require higher biosafety precautions for testing and would not be feasible for the target population more prone to severe MERS-CoV disease [27]. RBD-based vaccines are proposed to be more effective and safer than viral vector-based vaccines. Intranasal RBD-based immunization in animals elicits strong mucosal IgA responses as well as specific cell-mediated responses that may contribute to protection [28, 29]. Combination with adjuvants, such as aluminum or oil-based MF59,

has potential to increase effectiveness. However, evaluation of vaccine candidates in humans must be performed to better inform efficacy, and a vaccination platform that induces both humoral and cellular immune response could be rationalized.

Multiple vaccine platforms are in various preclinical testing stages [25], with a few vaccine candidates advancing into Phase 1 clinical testing. GLS-5300 (GeneOne Life Science, Inc.), which is comprised of an identical DNA plasmid as INO-4700, is a DNA-based vaccine targeting MERS-CoV S protein and has been evaluated in a completed Phase 1 intramuscular dose-ranging study in healthy adults (clinicaltrials.gov NCT02670187) [30], described further in Section 1.3.1. A second, Phase 1/2a study of GLS-5300 is ongoing to evaluate the safety and immunogenicity of intradermal administration (clinicaltrials.gov NCT03721718), described further in Section 1.3.1. Preclinical studies of GLS-5300 in mice, camels and non-human primates (NHPs) have demonstrated induction of neutralizing antibodies and antigen-specific cellular immune responses. Of note, vaccination in NHPs was able to protect from MERS-CoV challenge as immunized animals lacked respiratory distress and interstitial infiltrates, had normal lung histology and cleared viral loads [31].

1.2.3 Emerging Health Threat

Since 2012, the World Health Organization (WHO) has received over 2,400 laboratory-confirmed reports of individual cases and clusters of infection, including over 800 fatalities, across 27 countries (Saudi Arabia accounting for 80% of human cases) [32]. The latest WHO-reported crude fatality rate is 35.5% [33]. Although the majority of research has focused on symptomatic patients, more than 62% of these individuals may remain unidentified or undetected or display only mild symptoms [34], thus the number of confirmed cases may be greatly under-reported. Not only is continued development of enhanced detection and active surveillance programs warranted, but also more effective therapeutic options are required to manage existing infections and limit spread of disease. In support of continued advancements to address this serious global health concern, the Coalition for Epidemic Preparedness Innovations (CEPI) has assigned priority disease designation to developing a MERS-CoV vaccine [35], and the WHO has initiated a blueprint for preparatory and responses efforts [36].

1.3 Rationale

No investigational interventions have clearly and consistently demonstrated clinical benefit in MERS-CoV-infected patients, thus highlighting the continued unmet need for effective therapeutic and preventive solutions. INO-4700 is being evaluated for both routine prophylaxis and use during an outbreak situation. Since the RBD domain within the MERS-CoV S protein is highly mutable, INO-4700 has been designed to encode consensus sequences of the full length S protein covering multiple epitopes in order to induce broad cross-reactive immune responses. The INO-4700 plasmid, which is identical to GLS-5300, and the plasmid DNA backbone has been tested in previous clinical trials [30, 37-40]. Previous experience with plasmids similar to INO-4700 has demonstrated tolerability and both clinically relevant and immunogenic responses.

1.3.1 Dose and Regimen Rationale

INO-4700 is identical to the previously evaluated GLS-5300, except that it is formulated at a higher concentration. In a completed Phase 1 clinical trial, intramuscular (IM) dose-ranging administration of GLS-5300 delivered via EP in healthy adults was well-tolerated and induced seroconversion and T cell responses [30]. This study evaluated three different dose groups (0.67 mg, 2 mg, and 6 mg) administered IM in a three-immunization regimen

at Weeks 0, 4 and 12 in 75 healthy adult participants. Overall, transient local injection site discomfort and reactions were most commonly reported, consistent with previously published clinical trial reports of Inovio's DNA delivered via EP platform. The most common solicited systemic adverse event was headache, followed by malaise and myalgia, most of which were mild. Laboratory abnormalities were uncommon, and no grade 3 or higher laboratory abnormalities were deemed related to the vaccine. No vaccine-related serious adverse events were reported. The vaccine was immunogenic in all dosing groups with remarkably similar antibody and neutralization titers between all three doses. These levels were comparable to those observed in convalescent patients who have recovered from MERS-CoV infection. Furthermore, the vaccine generated long-lasting T cell responses that maintained average levels higher than convalescent patients for at least 60 weeks. Flow cytometry analysis and intracellular cytokine staining detected increases in $CD8^+$ T cells secreting IFNγ and TNFα and $CD4^+$ T cells secreting TNFα. In summary, the data from this first Phase 1 trial supports the strong immunogenicity of the vaccine and ability to induce durable immune responses for at least 1 year.

In an ongoing Phase 1/2a dose-ranging clinical trial, the safety, tolerability and immunogenicity of GLS-5300 delivered intradermally (ID) followed by EP in 60 healthy volunteers is being evaluated. Dose levels include 0.3 mg administered in a three-immunization regimen at Week 0, 4 and 12, 0.6 mg administered in a three-immunization regimen at Week 0, 4 and 12, and 0.6 mg administered in a two-immunization regimen at Week 0 and 8. As of June 2019, there have been no reports of treatment-associated serious adverse events and the majority of adverse events reported have been grade 1 or grade 2 in severity. Adverse event data standardization is in progress, but the most commonly reported adverse events are similar to that reported in the completed Phase 1 trial.

An interim analysis has showed that ID delivery of GLS-5300 induced a robust binding antibody and IFNγ cellular immune response in humans. A dose response was observed, such that the 0.6 mg dose induced significantly higher humoral and cellular immune responses. The 0.6 mg dose induced up to a 76% seroconversion rate following a single immunization, 88% seroconversion following the second immunization, and 100% seroconversion following the third. The 0.6 mg dose also induced robust cellular immune responses, with 56% responders after the second immunization and 78% responders after the third. The two-immunization regimen (Week 0 and 8 dosing) appeared to induce significantly higher antibody titers than the three-immunization regimen (Week 0, 4 12) as early as 2 weeks post second immunization, without affecting the cellular immune response. The overall response rate for the 0.6 mg dose, three-immunization regimen reached 92% after two immunizations and increased to 100% following the third immunization. The 0.6 mg dose, two-immunization regimen reached an overall response rate of 96% after only two immunizations.

Results from the complete Phase 1 clinical trial as well as interim safety and immunogenicity results from the ongoing Phase 1/2a clinical trial support continued evaluation of this plasmid in a demographically relevant population.

Intradermal delivery has been shown to be a more tolerable route of administration that induces superior humoral immune responses for previously evaluated DNA vaccines targeting viruses such as Ebola, Zika and HIV [39-41].

As such, Part I of the current clinical trial represents the dose-finding phase of the study to supplement previously amassed safety and immunogenicity data. Participants in Part 1 will receive dosing on Day 0 and Week 4 or Week 8, with a starting dose of INO-4700 of

0.6 mg, which demonstrated robust immunogenicity in the Phase 1/2a trial of GLS-5300 delivered ID followed by EP.

Furthermore, a long-term kinetic study of serologic responses from patients who recovered during the 2015 South Korea outbreak reports more rapid waning of antibody response during the first 6 months of disease onset that stabilizes between 6 months to 1 year [42]. Similarly, a study of survivors from the 2014 Saudi Arabia outbreak reports fewer patients with positive antibody response at 10 months following disease onset compared to 3 months [43]. As this data may indicate variable response over time, participants in Part 2 will receive dosing on Day 0 and Week 4 or 8 and a booster dose at Week 48 (only for the first 225 participants). Part 2 will thus confirm the optimal dose identified in Part 1 and will serve to also evaluate the impact of a booster/third dose.

Based on the at-risk population, active immunization should demonstrate ability to drive clinically relevant immune responses within 4-6 weeks of administration with long-term protection. Additionally, the WHO target product profile for a MERS-CoV vaccine suggests dosing regimens of no more than 3 doses in prophylactic settings and no more than 2 doses in reactive settings, with short intervals between doses [44].

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 [45-54]. 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 [53, 55] In many cases, protection from disease in animal models has also been demonstrated.

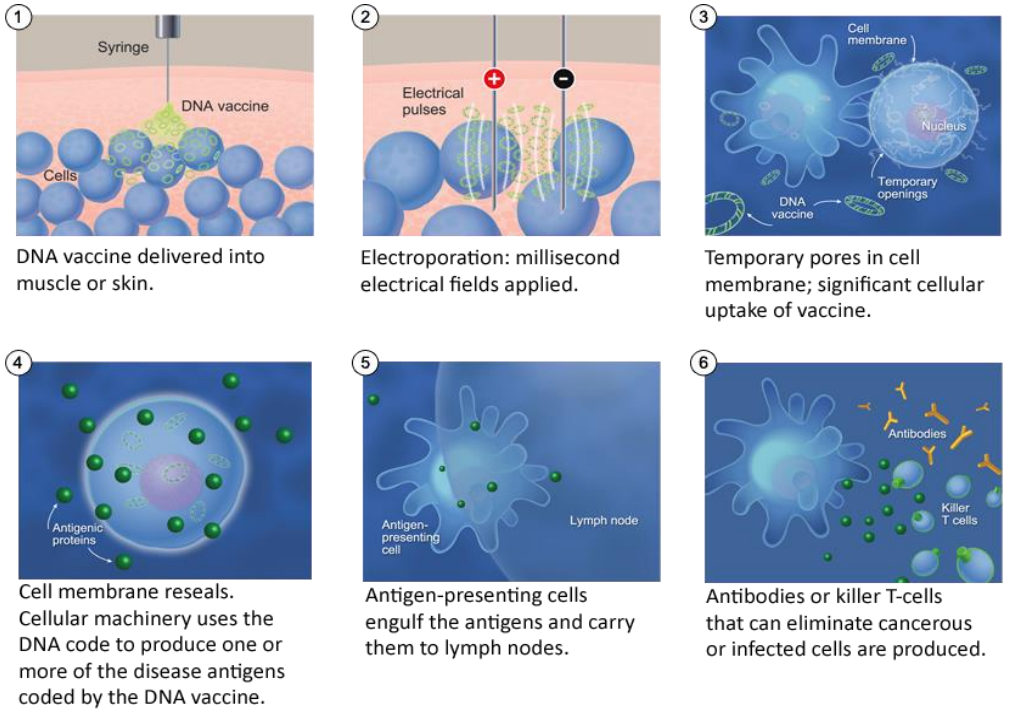
DNA vaccines are able to generate both $CD4^+$ and $CD8^+$ T cell responses. The ability to generate MHC-Class I restricted $CD8^+$ T cells (cytolytic T lymphocytes), which generally are not made following administration of inactivated viruses, proteins or peptides, may be important for key responses 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 [56]. 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. 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 [57]. 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 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 [58]. 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 [58] for the activation of both cellular and humoral responses [59, 60]. Importantly, immune responses generated by DNA vaccines delivered with EP are far superior to responses to the same vaccines delivered without EP [60]. 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 [61, 62].

The Inovio Pharmaceuticals constant current EP device [58] 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-4700 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) [40].

Figure 2: How Electroporation Works in the Body



1.4 POTENTIAL BENEFITS AND RISKS

As of September 30 2019, a total of 75 participants have been dosed with INO-4700 IM and 60 participants with INO-4700 ID. In studies of INO-4700 administered IM followed by EP using CELLECTRA™ 2000 devices in healthy volunteers the most frequently reported AE has been injection site pain (94.7%), of which all were Grade 2 or less. In the ongoing

study of INO-4700 administered ID followed by EP using CELLECTRA™ 2000 devices in healthy volunteers, the most frequently reported AE has been erythema (63.3%), of which all were Grade 1 (taken from unvalidated data as a preliminary analysis).

No specific AE has been identified as a risk. There may be potential benefit for prevention of MERS infection in affected areas, but efficacy is still unknown. Data gathered in this trial will be useful for future development of this vaccine for MERS-CoV.

Additional details regarding the benefits and risks for participants 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 INO-4700 in a demographically relevant population with the eventual goal of preparation for both routine prophylaxis and use during an outbreak situation.

2.1 HYPOTHESIS

A selected optimal dose of INO-4700 delivered ID followed by EP using CELLECTRA™ 2000 in healthy volunteers will be well tolerated, exhibit an acceptable safety profile and result in generation of immune responses to MERS-CoV.

3.0 CLINICAL TRIAL DESIGN AND ENDPOINTS

This is a Phase 2a, randomized, blinded, placebo-controlled, multi-center trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered by ID injection followed by EP using the CELLECTRA™ 2000 device in healthy adult volunteers. The primary objectives of this trial are to evaluate the tolerability, safety and immunogenicity of INO-4700 administered by ID injection followed by EP in healthy adult volunteers according to the regimens outlined in Table 1, Table 2, Table 3 and Figure 1.

Approximately 542 healthy volunteers will be evaluated across two (2) parts of this study, Part 1 and Part 2. INO-4700 or placebo (SSC-0001) will be administered ID in ~0.1 mL dose volume followed immediately by EP.

Part 1 – Dose Finding

In Part 1, approximately 192 participants ages 18-50 years will be assessed through five (5) dose levels and regimens. These five (5) dose levels and regimens will be evaluated across nine (9) groups designated Study Groups A, B, C, D, E, F, G, H and I. Study Groups A, B, C, D and E will receive INO-4700 and enroll approximately 32 participants per group. Study Groups F, G, H and I will receive placebo and enroll approximately 8 participants per group.

Participants will be randomized to receive either INO-4700 or placebo according to the dosing schedule described in Table 1. All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo) within each Study Group, with the exception of the site's pharmacy personnel.

Enrollment into all Study Groups will proceed in parallel. After the first four (4) participants in Active Study Groups and the first two (2) participants in Placebo Study Groups have Week 2 clinical laboratory and adverse event data available, the results will be reviewed by the DSMB (Figure 1). Enrollment will not be paused during this DSMB review, and screening and randomization may continue.

Upon completion of the Week 10 visit and availability of immunological data, Part 1 will be unblinded in order to allow for one regimen to be selected for advancement into Part 2. The Study Group with an optimal immune response, an acceptable safety profile and tolerant dosing regimen by Week 10 will be selected for Part 2. The Sponsor will remain blinded through Part 1 of the study until initiation of the Week 10 data review.

All Part 1 participants will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

Part 2 – Expansion

In Part 2, approximately 350 participants will be evaluated across one (1) dose level and regimen as outlined in Table 2 and Table 3. The dose level and regimen will be identified based on the optimal dose selection from Part 1. Enrollment into Part 2 may begin following completion of the Week 10 optimal dose and regimen selection in Part 1 (i.e., prior to Week 48 completion in Part 1).

In Part 2A, participants will be randomized to receive the optimal dose of active (INO-4700) selected in Part 1 of this study or placebo (SSC-0001) (Figure 1). Approximately 300 participants will receive INO-4700 and 50 participants will receive placebo.

In Part 2B, the first 200 participants randomized to the Part 2A Active Study Group will receive a third dose of either INO-4700 or placebo at Week 48. Specifically, Study Group "Active – Booster" will receive INO-4700 at the first (Day 0), second (Week 4 or 8) and third (booster at Week 48) doses. Study Group "Active – Placebo" will receive INO-4700 at the first (Day 0) and second (Week 4 or 8) doses, and placebo at the third (Week 48) dose. Similarly, in Part 2B, the first 25 participants randomized to the Part 2A Placebo Study Group will receive a third dose of placebo at Week 48. Collectively, these first 225 participants will be followed for 68 weeks from the Day 0 dosing [i.e., Week 68 will be the planned End of Study (EOS) visit]. All remaining 125 participants in Part 2A (i.e., those receiving only 2 doses) will be followed for 48 weeks from the Day 0 dosing [i.e., Week 48 will be the planned End of Study (EOS) visit].

All participants and all clinical site staff will remain blinded to the subject treatment allocation (i.e., INO-4700 or placebo), with the exception of the site's pharmacy personnel. Enrollment into Active and Placebo Study Groups will proceed in parallel. No enrollment pauses are planned.

Upon completion of the Week 12 visit and availability of immunological and safety data, group-level (INO-4700 or placebo) unblinded summaries of immunogenicity and safety will be produced. This Week 12 analysis will serve to inform product development goals. The Sponsor will continue to remain blinded to subject-level treatment allocation (i.e., INO-4700 or placebo) for the remainder of the trial.

DSMB for Parts 1 and 2

The DSMB will remain unblinded throughout the duration of the study.

In Part 1, the DSMB will review clinical laboratory and adverse event data for the first six (6) participants, 4 active and 2 placebos, in each Active and Placebo Study Group, respectively, after the Week 2 safety data are complete. The DSMB will again convene to review all available safety data for all Study Groups after approximately 50% of planned participants are enrolled (i.e., approximately 96 participants), and after enrollment is complete.

Subsequently, the DSMB will convene approximately every three (3) calendar months thereafter until study completion. Enrollment pauses are not planned during any DSMB review in Part 1 nor 2.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified immediately, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

3.1 PRIMARY OBJECTIVES

- Evaluate the tolerability and safety of INO-4700 administered by ID injection followed by EP in healthy adult volunteers
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for identification and confirmation of an optimal dose and regimen
- Evaluate selected optimal dose for safety and immunogenicity

3.2 PRIMARY ENDPOINTS

Safety Endpoints:

- Incidence of adverse events by system organ class (SOC), preferred term (PT), severity and relationship to investigational product
- Administration (i.e., injection) site reactions (described by frequency and severity)
- Incidence of adverse events of special interest

Immunogenicity Endpoints:

- Overall Immune response
  - MERS-CoV antigen specific antibodies
  - Antigen-specific cytokine-producing T cell responses

3.3 EXPLORATORY OBJECTIVE

- Evaluate the expanded immunological profile by assessing both T and B cell immune responses
- Evaluate the cellular (T cell) and humoral immune response to INO-4700 administered by ID injection followed by EP for impact of boosting with a third dose
- Evaluate humoral immune response cross reactivity to other coronaviruses

3.4 EXPLORATORY ENDPOINT

- Expanded immunological profile which may include (but not limited to) additional assessment of T and B cell numbers and T and B cell molecular changes by measuring immunologic proteins and mRNA levels of genes of interest at all weeks as determined by sample availability
- Antibodies to other coronaviruses

3.5 SAFETY ASSESSMENT

For Part 1, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6, Week 10 and Week 48. For Part 2, adverse events will be collected at every visit and safety samples will be drawn at Screening, Week 2, Week 6 (if optimal regimen includes dosing at Week 4), Week 10 (if optimal regimen includes dosing at Week 8), Week 48, Week 50 (for participants receiving three doses) and Week 68 (for participants receiving three doses). Refer to the Schedule of Events

Table 4, Table 5 and Table 6 for additional details.

For both Parts 1 and 2, all adverse events, regardless of relationship, will be collected from the time of consent until study discharge.

Additionally, for both Parts 1 and 2, a pregnancy test will be performed at screening and prior to each dose.

3.6 IMMUNOGENICITY ASSESSMENT

For Part 1, immunology blood samples will be collected at Screening, Day 0, Week 6, Week 10and Week 48. For Part 2, immunology blood samples will be collected at Screening, Day 0, Week 6 (if optimal regimen includes dosing at Week 4), Week 8 (if optimal regimen includes dosing at Week 8), Week 10 (if optimal regimen includes dosing at Week 8), Week 12 (if optimal regimen includes dosing at Week 4), Week 48, Week 50 (for Part 2B participants receiving three doses) and Week 68 (for Part 2B participants receiving three doses). Refer to the Schedule of Events Table 4, Table 5 and Table 6 for additional details. Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

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. For Part 1, adults age 18 and 50 years, inclusive. For Part 2, adults at least 18 years of age;
c. Judged to be healthy by the Investigator on the basis of medical history, physical examination and vital signs performed at Screening. **Note:** Participants taking daily prescription or non-prescription medications for management of acceptable chronic medical conditions must be on a stable dose, as defined by non-change in dose for the 3 months prior to the first dose of study medication and no planned changes during the active dosing period of the study;
d. Able and willing to comply with all study procedures;
e. Screening laboratory results within normal limits for testing laboratory or deemed not clinically significant by the Investigator;
f. Negative serological tests for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and Human Immunodeficiency Virus (HIV) antibody or rapid test at screening;
g. Screening ECG deemed by the Investigator as having no clinically significant findings (e.g. Wolff-Parkinson-White syndrome);
h. Must meet one of the following criteria with respect to reproductive capacity:
    - Women who are post-menopausal as defined by spontaneous amenorrhea for ≥ 12 months;
    - Surgically sterile or have a partner who is sterile (i.e., vasectomy in males at least six (6) months prior to enrollment or tubal ligation, absence of ovaries and/or uterus in females);
    - 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. Pregnant or breastfeeding, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit until 3 months following last dose;
b. Positive serum pregnancy test during screening or positive urine pregnancy test prior to dosing;
c. History of respiratory diseases such as asthma, chronic obstructive pulmonary disease or chronic bronchitis;
d. Is currently participating in or has participated in a study with an investigational product within 30 days preceding Day 0;
e. Previous receipt of any vaccine within 30 days preceding Day 0 or planning to receive any vaccine during the timeframe restricted per the protocol;
f. Previous receipt of an investigational vaccine product for prevention of MERS;
g. Prior exposure to MERS-CoV or camels (serology or antibody testing will be requested at the Investigator's discretion);
h. Participants who participated in MERS-201 Part 1 cannot participate in MERS-201 Part 2;
i. Fewer than two acceptable sites available for ID injection and EP considering 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. Prisoner or participants who are compulsorily detained (involuntary incarceration);
k. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids) prior to dosing. Systemic corticosteroids must be discontinued at least 3 months prior to first dose;
l. Reported active drug or alcohol or substance abuse or dependence.

4.3 DISCONTINUATION/WITHDRAWAL OF CLINICAL TRIAL PARTICIPANTS

Participants 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 withdraw 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 discontinues from the trial or is withdrawn from the trial prior to trial completion, all applicable activities scheduled for the final trial visit (i.e., Part 1 Week 48 EOS or Part 2 Week 48 or 68 EOS) should be performed at the time of discontinuation. Any AEs 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: Safety Data Reporting Period, Method of Collection and Submission.

Unless a subject refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events (Tables 3, 4 and 5) following the last dose whether or not the subject has completed all doses.

Reasons for 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 participants who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate eCRF. However, participants 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.

Subject dosing may be discontinued if they experience any of 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

Subjects who discontinue or withdrawal from the study will not be replaced.

5.0 CLINICAL TRIAL TREATMENT

5.1 INVESTIGATIONAL PRODUCTS (IPS) AND STUDY DEVICE

5.1.1 INO-4700 AND SSC-0001

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-4700 is the active investigational product to be used in this study. The INO-4700 drug product contains 10 mg/mL pGX9101 in 1X SSC buffer (150 mM sodium chloride and 15 mM sodium citrate). A volume of 0.4 mL will be filled into 2-mL glass vials that are fitted with rubber stoppers and sealed aluminum caps. INO-4700 must be placed in 2–8°C storage immediately upon arrival and requires preparation prior to administration, which is outlined in the pharmacy manual.

pGX9101 is a DNA plasmid expressing a synthetic consensus (SynCon®) Middle East Respiratory Syndrome Human Coronavirus Spike protein (MERS-CoV Spike), driven by a human CMV promoter (hCMV promoter), and with the bovine growth hormone 3' end poly-adenylation signal (bGH polyA). The pGX0001 backbone includes the kanamycin resistance gene (KanR) and plasmid origin of replication (pUC ori).

Sterile saline sodium citrate (SSC) buffer (SSC-0001), which contains sterile 150 mM sodium chloride and 15 mM sodium citrate in 2-mL or 10-mL glass vials, stoppered, and sealed with aluminum caps, will be used as the placebo at the clinical site.

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 TREATMENT REGIMENS

- Part 1 Group A – One 0.6 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group B – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group C – One 1.0 mg ID injection of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group D – Two 0.5 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group E – Two 1.0 mg ID injections (in an acceptable location on two different limbs) of INO-4700 followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group F – One ID injection of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 1 Group G – One ID injection of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group H – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 8 (± 5 days)
- Part 1 Group I – Two ID injections (in an acceptable location on two different limbs) of placebo followed by EP administered at Day 0 and Week 4 (± 5 days)
- Part 2 – Dose and regimen to be determined, each ID injection(s) followed by EP administered at Day 0, Week 4 or Week 8, and Week 48 (for Part 2B participants receiving a third dose)

INO-4700 or placebo will be administered intradermally in ~0.1 mL dose volume followed immediately by EP.

5.2.1 BLINDING

This trial is randomized across Study Groups, is blinded to the Investigator and subject, and is placebo-controlled with blinding throughout the duration of the trial as described in Section 3: Clinical Trial Design and Endpoints. There is no difference in appearance between INO-4700 and SSC-0001; however, they may be packaged in different sized vials. To maintain the blind, vials will only be handled by designated unblinded personnel (site pharmacist) at the site. The Sponsor will also be blinded as described in Section 3: Clinical Trial Design and Endpoints.

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) with the study product 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-4700 / SSC-0001

This trial is randomized and blinded across study groups and placebo-controlled. Therefore, the subject and the Investigator's clinical site personnel (except for the site pharmacy) are blinded to INO-4700 and SSC-0001. Each vial of investigational product will be labeled consistent with the example product label provided in Table 7 and Table 8).

Table 7: Investigational Labels for INO-4700 Drug Product and SSC-001 on Vials

Protocol Number ID: MERS-201 INO-4700 (10 mg/mL) 0.4mL/Vial Single Use Vial Solution for Intradermal injection Lot: Date of Manufacture: Expiry Date: Store at 2-8°C CAUTION: New Drug for Investigational Use Only. INOVIO PHARMACEUTICALS, USA Treatment No. _____ Subject No. _____	Protocol Number: MERS-201 Sterile SSC Buffer for Dilution SSC-0001 (X mL/Vial) Solution for Intradermal injection Lot: Date of Manufacture: Expiry Date: Store at 2-8°C CAUTION: New Drug for Investigational Use Only. INOVIO PHARMACEUTICALS, USA Treatment No. _____ Subject No. _____

Table 8: Investigational Labels for INO-4700 Drug Product and SSC-0001 on Cartons

Protocol Number: MERS-201 INO-4700 (10 mg/mL) Lot: Date of Manufacture: Expiry Date: 0.4mL/Vial Single Use Vial Solution for Intradermal injection. Use in accordance with protocol. Storage Condition: Store between 2-8°C. Do not freeze. CAUTION: New Drug for Investigational Use Only. Keep out of reach of children. Sponsor: Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110, Plymouth Meeting, PA 19462 USA Phone: +1-267-440-4257 The package is intended for export from the United States. Treatment No. _____ Investigator Name _____ Subject No. _____ Visit No.: _____ Visit Date: _____	Protocol Number: MERS-201 Sterile SSC Buffer for Dilution SSC-0001 (X mL/Vial) Lot: Date of Manufacture: Expiry Date: Solution for Intradermal injection. Use in accordance with protocol. Storage Condition: Store between 2-8°C. Do not freeze. CAUTION: New Drug for Investigational Use Only. Keep out of reach of children. Sponsor: Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110, Plymouth Meeting, PA 19462 USA Phone: +1-267-440-4257 The package is intended for export from the United States. Treatment No. _____ Investigator Name_____ Subject No. _____ Visit No.: _____ Visit Date: _____

5.3.2 CELLECTRA™ 2000

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

The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, potential risks and adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA™ 2000 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-4700 AND SSC-0001

INO-4700 and SSC-0001 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 unblinded 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-4700 is supplied in single dose 2-mL vials at a concentration of 10 mg/mL at a minimum volume of 0.4 mL. SSC-0001 is supplied in 2-mL or 10-mL vials at a minimum volume of 1.1 mL or 2 mL.

Blinded staff involved in the clinical execution of the study should not come in contact with vials of INO-4700 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 fill INO-4700 or SSC-0001 into a blinded syringe in accordance with the subject's randomization code. The syringe will be transferred to blinded site personnel for administration. The preparation and dispensing information is provided in the Pharmacy Manual. A randomization schedule will be generated by the Sponsor statistician.

5.6 USE OF STUDY DEVICE

The CELLECTRA™ 2000 is an investigational 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 INO-4700 AND SSC-0001 ACCOUNTABILITY

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

5.7.2 CELLECTRA™ 2000 ACCOUNTABILITY

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

For each subject administration, there must be a record of each product used for that participant, i.e., CELLECTRA™ 2000 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-4700 AND SSC-0001

Upon completion or termination of the study, all unused IP (INO-4700 and SSC-0001) 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 IP vials 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. All precautions must be taken to maintain blind throughout this process. If requested by the Sponsor, the return of unused IP should be arranged by the responsible Inovio Representative. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. personnel or designated unblinded Clinical Monitor. If IP is 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 unblinded 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 trial Schedule of Events (Tables 4, 5 and 6) in the Clinical Protocol Synopsis summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator. A 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 study 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. Participants' post-menopausal status must meet requirements as

specified in the inclusion criteria [63, 64]. The following screening evaluations will be performed within 60 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study IP administration.

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

- Signed and dated informed consent (Section 6.2);
- Review and confirm all inclusion/exclusion criteria (Section 4.1 and 4.2);
- Obtain and document complete medical history, surgical history (including all past procedures), present conditions and concomitant illnesses (Section 6.1.1.1);
- Collect demographics, including gender, 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 including body weight and height, heart rate (HR), respiratory rate (RR), blood pressure (BP) and oral temperature (Section 6.4);
- Collect blood for CBC with differential, serum chemistry (sodium [Na], potassium [K], chloride [Cl], bicarbonate [HCO_3 or CO_2], calcium [Ca], phosphate [PO_4], glucose, blood urea nitrogen [BUN] and creatinine [Cr]) and liver function [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] (Section 6.4);
- Perform 12 lead ECG (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect blood for serum pregnancy test (Section 6.4);
- Collect serum for MERS-CoV (per PI discretion), HIV, Hepatitis B surface antigen (HBsAg) and Hepatitis C serology (Section 6.4) per national guidelines;
- Collect whole blood and serum for immunology assessment (Section 6.4.6). At the investigator's discretion, this sample collection may be postponed to Day 0, at which time both the screening and Day 0 samples would be collected prior to dosing.

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 or new treatments taken at or after the signing of the informed consent, should be recorded in the CRF as concomitant medications.

6.1.2 Clinical Trial Evaluations and Procedures

Once eligibility has been confirmed, the participant will be assigned to receive IP. Visit dates and windows must be calculated from Day 0, unless otherwise noted. All study groups in Part 1 will be followed until Week 48, booster dose participants in Part 2 will be

followed to Week 68 and all other participants in Part 2 who did not receive booster dose will be followed to Week 48. All participants will be followed in accordance with assessments outlined below.

6.1.2.1 Day 0

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

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- 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 immunology assessment (Section 6.4.6).

The following evaluation will be performed on **Day 0 prior to EP:**

- Assess for injection site for IP leakage (Section 6.4.1)

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

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

6.1.2.2 Week 2

Calculated from Day 0, the following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);

6.1.2.3 Week 4

Part 1

The following evaluations will be performed on **Week 4 (complete prior to IP administration for Part 1 Study Groups A, B, E, F and I):**

- Collect all present and/or new or ongoing adverse events;
- 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) for Part 1 Study Groups A, B, E, F and I only.

The following evaluation will be performed on **Week 4 prior to EP (for Part 1 Study Groups A, B, E, F and I only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 4 after IP administration (for Part 1 Study Groups A, B, E, F and I only)**:

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

Part 2 if Day 0/Week 4 Dosing Regimen is Optimal

The following evaluations will be performed on **Week 4 (complete prior to IP administration if following Table 5):**

- Collect all present and/or new or ongoing adverse events;
- 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).

The following evaluation will be performed on **Week 4 prior to EP (if following Table 5 only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 4 after IP administration (if following Table 5 only)**:

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

Part 2 if Day 0/Week 8 Dosing Regimen is Optimal

The following evaluation will be collected on **Week 4 (if following Table 6 only)** during a follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

6.1.2.4 Week 6

Calculated from Week 4 if Week 4 is a dosing visit, the following evaluations will be performed at this visit for **Part 1 and Part 2 if Day 0/Week 4 dosing regimen is optimal**:

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.5 Week 8

Part 1

The following evaluations will be performed on **Week 8 (complete prior to IP administration for Part 1 Study Groups C, D, G and H):**

- Collect all present and/or new or ongoing adverse events;
- 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) for Part 1 Study Groups C, D, G and H only.

The following evaluation will be performed on **Week 8 prior to EP (for Part 1 Study Groups C, D, G and H only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 8 after IP administration (for Part 1 Study Groups C, D, G and H only)**:

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

Part 2 if Day 0/Week 4 Dosing Regimen is Optimal

The following evaluation will be collected on **Week 8 (if following Table 5 only)** during a follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

Part 2 if Day 0/Week 8 Dosing Regimen is Optimal

The following evaluations will be performed on **Week 8 (complete prior to IP administration if following Table 6):**

- Collect all present and/or new or ongoing adverse events;
- 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 immunology assessment (Section 6.4.6).

The following evaluation will be performed on **Week 8 prior to EP (if following Table 6 only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 8 after IP administration (if following Table 6 only)**:

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

6.1.2.6 Week 10

Calculated from Week 8 if Week 8 is a dosing visit, the following evaluations will be performed at this visit for **Part 1 and Part 2 if Day 0/Week 8 dosing regimen is optimal**:

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.7 Week 12

Part 1

The following evaluations will be collected during the follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

Part 2 if Day 0/Week 4 Dosing Regimen is Optimal

The following evaluations will be performed at this visit:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

Part 2 if Day 0/Week 8 Dosing Regimen is Optimal

The following evaluations will be collected during the follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

6.1.2.8 Week 30

The following evaluations will be collected during the follow-up phone call visit:

- Collect all present and/or new or ongoing adverse events.

6.1.2.9 Week 48

Part 1

The following evaluations will be performed at this visit (End of Study visit):

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

Part 2

The Week 48 visit will be the End of Study visit for participants receiving only two doses. The Week 48 visit will be the last dosing visit for participants receiving three doses. The

following evaluations will be performed on **Week 48 (complete prior to IP administration for Part 2 participants receiving a third/booster dose)**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Targeted physical examination (Section 6.4) for Part 2 participants receiving a third/booster dose;
- Full physical examination (Section 6.4) for Part 2 participants receiving two doses only;
- Record vital signs (Section 6.4);
- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect urine for urine pregnancy test (Section 6.4) for Part 2 participants receiving a third/booster dose;
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

The following evaluation will be performed on **Week 48 prior to EP (for Part 2 participants receiving a third/booster dose only):**

- Assess for injection site for IP leakage (Section 6.4.1)

The following evaluations will be performed on **Week 48 after IP administration (for Part 2 participants receiving a third/booster dose only)**:

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

6.1.2.10 Week 50

Calculated from Week 48. The following evaluations will be performed at this visit **only for Part 2 participants receiving a third/booster dose:**

- Collect all present and/or new or ongoing adverse events;
- 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, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.1.2.11 Week 68

The following evaluations will be performed at this visit (End of Study Visit) **only for Part 2 participants receiving a third/booster dose**:

- Collect all present and/or new or ongoing adverse events;
- Document any present conditions and concomitant illnesses;
- Record current concomitant medications/treatments (Section 6.4.7);
- Full physical examination (Section 6.4);
- Record vital signs (Section 6.4);

- Collect blood for CBC with differential, serum chemistry and liver function (Section 6.4);
- Collect urine for routine urinalysis (Section 6.4);
- Collect whole blood and serum for immunology assessment (Section 6.4.6).

6.2 INFORMED CONSENT

All participants 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 participants
- Explain the clinical trial
- Provide clinical trial participants 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 60 day screening window.

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).

Participants meeting eligibility criteria listed in the protocol will be randomized by a computer generated allocation schedule.

6.4 SAFETY EVALUATIONS

PHYSICAL EXAM AND TARGETED PHYSICAL ASSESSMENTS

A full physical examination will be conducted during Screening and at study discharge/End of Study visit (i.e., Week 48, Week 68 or any other study discontinuation visit). 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 oral temperature, respiration rate, blood pressure and heart rate will be measured at Screening and at select visits during the study.

HEIGHT AND WEIGHT

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

12-LEAD ECG

A single 12-lead ECG will be performed at Screening for all participants to determine eligibility. ECG results obtained within 60 days of Day 0 are acceptable. The ECG should include measurements of ventricular rate, PR, QRS, QT, QTcb or QTcf, as well as an assessment of whether the ECG is normal or abnormal. Abnormal ECGs should be interpreted as clinically significant or not clinically significant. Dosing will be delayed in the event of a clinically significant abnormal pre-dose ECG until it has been reviewed by the PI, qualified PI designee, MM or Sponsor consultant cardiologist and deemed safe to proceed.

LABORATORY EVALUATIONS

At Screening and select visits during the study, blood samples will be collected for safety and immunology assessments. Approximately 250 mL and 240-340 mL of blood will be drawn from each subject in Part 1 and Part 2, respectively, over the course of the study. Participants may be asked to come back 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 select visits during the study.

Serum chemistry:

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3 or CO2), Calcium (Ca), Phosphate (PO4)], glucose, BUN (blood urea nitrogen), and Creatinine (Cr) will be measured at Screening and select visits during the study.

Liver function:

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will be measured at Screening and select visits during the study.

Urinalysis:

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and select visits during the study. If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology:

Antibodies to MERS-CoV (per PI discretion), Hepatitis B surface antigen (HBsAg), Hepatitis C antibody and HIV antibody or rapid test will be measured at Screening only.

Pregnancy Testing:

For women of childbearing potential (WOCBP), a serum pregnancy test will be obtained at Screening and a urine pregnancy test will be performed prior to 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 participant is pregnant prior to completing the specified dose regimen, then no further IP

will be administered. Every attempt should be made to follow pregnant participants for the remainder of the study and to determine the outcome of the pregnancy.

6.4.1 INJECTION AND EP

Participants in Part 1 Study Groups A, B and C will receive one injection of INO-4700 in a volume of ~0.1 mL by ID injection above an acceptable muscle location for injection, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups D and E will receive two injections of INO-4700, each in a volume of ~0.1 mL, above an acceptable muscle location on two different limbs, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups F and G will receive one injection of placebo in a volume of ~0.1 mL by ID injection above an acceptable muscle location for injection, the injection site is assessed for IP leakage, and the injection is followed immediately by EP. Part 1 Study Groups H and I will receive two injections of placebo, each in a volume of ~0.1 mL, above an acceptable muscle location on two different limbs, the injection site is assessed for IP leakage, and the injection is followed immediately by EP.

Participants in Part 2 will receive one or two injections per dosing visit of the optimal dose of INO-4700 or placebo in volume of ~0.1 mL by ID injection above an acceptable skin location for injection, the injection site is assessed for IP leakage, and the injections is followed immediately by EP.

Only if the deltoid muscle is not a suitable location (see exclusion criterion ‘h’), 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, previous injection site at the same dosing visit, 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 ANXIETY AND PAIN DUE TO ELECTROPORATION (EP) PROCEDURES

Participants may be offered topical anesthetic (e.g., EMLA or equivalent) to prevent discomfort from the injection/EP procedure. If a topical anesthetic is used, an approximate 1.5 cm diameter amount will be applied without occlusion to the administration site ~30 minutes prior to injection/EP.

Participants may be offered a mild sedative (e.g., 0.5-1 mg lorazepam or equivalent) for anxiety related to the injection/EP procedure. Mild sedatives may be administered approximately 1 hour prior to injection/EP on dosing visits. Participants who receive a mild sedative must not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and should have arranged transportation to depart the study site.

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

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

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, liver function, and hematology and urinalysis performed at the visits listed in the Schedule of Events (Tables 3, 4 and 5) 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).

6.4.4 Assessment of Clinical Trial Adverse Events (AEs)

Participants 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. Participants 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 informed consent until study discharge. 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 9 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 9: 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 to assess overall immune response. Immunology blood and serum samples are to be collected at Screening and select visits during the study. Both Screening and Day 0 immunology samples are required to enable all immunology testing. However, at the Principal Investigator’s discretion, collection of the screening immunology samples may be postponed and collected along with the Day 0 samples. 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-4700 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.

An immune responder is defined as having either an increase in vaccine antibody titer compared to baseline or an increase in the number of vaccine specific IFN-gamma secreting cells as compared to baseline.

Determination of analysis of collected samples for immunological endpoints will be determined on an ongoing basis throughout the study.

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 the case report forms (CRFs).

Actual or estimated start and stop dates must be provided. This information will be obtained from the subject and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented.

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

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

Participants must not be vaccinated (e.g., influenza vaccine, COVID-19 vaccine) from 30 days prior to Day 0 until after completion of the study visit 2 weeks after the second dose of investigational product (i.e. the Week 6 visit if the second dose is at Week 4 and the Week 10 visit if the second dose is at Week 8). For Part 2B, receipt of other vaccinations is also prohibited from 2 weeks prior to the Week 48 visit through the Week 50 visit.

Participants must not receive a course of systemic corticosteroids (≥2 mg/kg of prednisone or equivalent for 5 days) within 3 months prior to any dose of investigational product.

Participants must not have fever (oral temperature >38.0 degrees Celsius or 100.4 degrees Fahrenheit) within 72 hours prior to each dose of investigational product.

7.0 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 SAFETY PARAMETERS

The safety of INO-4700 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 to have a causal relationship with this treatment.

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

Adverse Events (AEs) include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after screening (before the administration of clinical trial drug)
- Any pre-existing condition 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

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 participant 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 participant 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 participant'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 participant or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clarification of Serious Adverse Events (SAEs)

- Death in itself is not an AE. Death is an outcome of an AE, but when the cause of death has not been provided, use the event term: death of unknown cause.
- The participant 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 participants.

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.

7.8.1.1 Management of COVID-19 Infection and COVID-19 Immunization

COVID-19 is categorized as an Adverse Event of Special Interest (AESI). If a participant experiences symptoms suggestive of COVID-19, the participant should inform the Principal Investigator. Based on the assessment of the Principal Investigator and further investigation, participants with a confirmed COVID-19 diagnosis should be managed according to standard of care.

If the Principal Investigator believes that the participant should be managed beyond the routine care that can be provided by the study site, the participant should be referred to their primary health care provider or a medical treatment facility for further management. On recovery, the participant should continue with the study dosing and procedures if deemed fit by the Principal Investigator, in accordance with Section 4.3. If the participant is not deemed fit to continue dosing or to continue certain follow-up procedures, (e.g. blood draws), the investigator should continue to follow the participant for safety, performing those procedures deemed acceptable, through the remainder of the trial.

If participants are treated or hospitalized due to their illness and cannot return for follow-up visits, the study team should request COVID-19 specific test results, treatments, treatment outcomes and diagnostics. These results and diagnostics will be recorded in the safety database in accordance with Section 7.9.

For a participant that is scheduled to receive a COVID-19 vaccine, or has received the vaccine for COVID-19, all efforts should be made to remain within the timelines for vaccination outlined in Sections 4.2 and 6.4.8.

All efforts to continue study procedures must be undertaken by the site and the participant should be followed according to the protocol requirements for an AESI (Section 7.9).

7.8.2 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.

7.8.3 CLINICAL TRIAL STOPPING RULES

The stopping rules for this study are any of the following:

- Any study treatment-related SAE.
- Any Grade 4 toxicities related to study treatment.
- Any report of anaphylaxis from study treatment.

Should the criteria for any stopping rule be met, at any time, the DSMB will be notified, and the study may be paused or stopped if the DSMB considers the safety data unsatisfactory. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants to the study or Study Group(s).

7.9 SAFETY DATA REPORTING PERIOD, METHOD OF COLLECTION AND SUBMISSION

All AEs will be collected from the time informed consent is obtained until study discharge. This information will be captured in the Electronic Data Capture (EDC) system.

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

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

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 10: SAE Contact Information

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

Table 11: Medical Monitor Direct Contact Information

[redacted] MD
Email: [redacted]
Cell Phone: [redacted]

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

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

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

- Redact the medical records of all personal data (e.g., confidential subject data, Personal Identifying Information [PII])
- Provide the subject's assigned identification number (SID) on the records

All SAE and AESI information reported to Inovio will be entered into the Inovio safety database.

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 participants) 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 participant 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

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

All pregnancies that occur from the time of first administration of clinical trial treatment through study completion (Part 1 – Week 48 and Part 2 – Week 48 or Week 68) will be reported to the Sponsor. If clinical trial site staff become aware that a subject becomes pregnant after enrolling in the clinical trial, she will not be given any additional treatments with the IP. A Pregnancy Form will be completed by the PI and submitted to the Sponsor within 24 hours after becoming aware of the pregnancy.

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

The clinical trial site must request the subject's permission to query the subject for outcome of the pregnancy. For participants who provide permission, the clinical trial site will follow-up with the study participant regarding outcome of the pregnancy and the neonate's health out to 30 days post-delivery. The subject will continue to be followed for safety assessments without receiving additional IP until clinical trial discharge in accordance with this protocol. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. The PI should use clinical judgment regarding subsequent clinical trial-related blood collection based on the presence or absence of anemia in each subject.

Male participants 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 update the Pregnancy Form with information on the pregnant partner's health and the course and outcome of the pregnancy, including the neonate's health out to 30 days post-delivery, 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.

All pregnancy information reported to Sponsor will be entered into the Sponsor's safety database.

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

7.13 Notifying Regulatory Authorities and Institutional Review Boards (IRBs)/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 probably or possibly related to the clinical trial treatment, the PI should promptly document and report the event to the Sponsor. Additionally, if the trial is discontinued for any reason (Section 7.15), all enrolled subjects still participating in the study will undergo the end of study evaluation prior to discontinuation from the study and any reported SAE or AESI will be followed by the PI until resolution or return to baseline status, or stabilization of the reported event (i.e., the expectation that it will remain chronic).

7.15 CLINICAL TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the clinical trial at this site or at multiple sites for safety or administrative reasons at any time. In particular, a clinical trial site that does not recruit at a reasonable rate may be discontinued. Additionally, the clinical trial may be discontinued at any time by an IRB/REB/EC, INOVIO, or a regulatory authority as part of their duties to ensure that clinical trial participants 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 documentation of the statistical and analytical plan is presented below.

8.2 GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals, or its representative. This is a randomized across Study Group, investigator-and-participant blinded, placebo-controlled (SSC-0001), multi-center phase 2a trial to evaluate the safety, tolerability and immunological profile of INO-4700 administered in healthy adult volunteers. Approximately 542 volunteers will be evaluated across two (2) parts: Part 1 Dose Finding and Part 2 Expansion.

Approximately 192 participants in Part 1 will be randomized across each group (A through I; see Table 1) to receive either INO-4700 or placebo. Upon completion of the Week 10 visit by all Part 1 participants including evaluable immunological data from all Study Groups, one optimal Study Group dose and regimen will be selected for expansion into Part 2. Participants in Part 1 will be followed until Week 48.

Approximately 350 participants in Part 2 will be randomized to receive the optimal dose of INO-4700 or placebo (see Table 2). The first 225 participants randomized in parallel to three Study Groups will receive a third dose of either INO-4700 or placebo at Week 48. Participants will either receive a week 48 active treatment administration on top of their two prior active treatment administrations (N=100), or a week 48 placebo administration on top of their two prior active treatment administrations (N=100) or a week 48 placebo administration on top of two prior placebo administrations (N=25). Collectively, these first 225 participants will be followed until Week 68. The remaining 125 participants will be randomized in parallel to either 2 active treatment administrations (N=100) or 2 placebo administrations (N=25) and followed until Week 48.

Details on the Study Group design and conduct and frequency of DMSB meetings can be found in Sections 3.0 and 12.1.

The trial's primary analyses pertains to the evaluation of the tolerability, safety and overall immune response to INO-4700 administered by ID injection followed by EP in healthy volunteers. Exploratory analyses concern the evaluation of the expanded immunological response to INO-4700 delivered by ID injection followed by EP, the cellular (T cell) and humoral immune response to boosting with a third INO-4700 ID injection followed by EP and the evaluation of the cross reactivity of other coronavirus spike proteins to the humoral

immune response to the MERS-CoV spike protein after receipt of the INO-4700 ID injection followed by EP.

8.3 STATISTICAL HYPOTHESES

No formal statistical hypothesis will be tested in Part 1 of this trial. The hypothesis in Part 2 of this trial is H0: $p \leq 70\%$ versus H1: $p > 70\%$, where p denotes the true population overall immunological response rate for the selected optimal dose of INO-4700.

8.4 ANALYTICAL POPULATIONS

Analysis populations will be:

The modified intention to treat (mITT) population includes all participants who receive at least one dose of the INO-4700 or placebo. Participants in this sample will be analyzed by their original assigned dose of INO-4700 or placebo. The mITT population will be used to analyze co-primary and exploratory immunological endpoints.

The per-protocol (PP) population is comprised of mITT participants who receive all their planned administrations and who have no Medical Monitor-assessed important protocol violations. Analyses on the PP population will be considered supportive of the corresponding mITT analyses. Participants excluded from the PP population will be identified and documented prior to locking the study database.

The safety analysis population includes all participants who receive at least one dose of INO-4700 or placebo administered by ID injection. Participants for this population will be grouped in accordance with the dose of INO-4700 or placebo that they received. This population will be used for all safety analyses in the study.

8.5 DESCRIPTION OF STATISTICAL METHODS

8.5.1 PRIMARY SAFETY ANALYSES

The primary analyses for this trial are safety analyses of treatment emergent adverse events (TEAEs), administration site reactions and clinically significant changes in safety laboratory parameters from baseline.

TEAEs are defined for this trial as any AEs/AESIs/SAEs that occur on or after Day 0 following IP administration. All TEAEs will be summarized by frequency, percentage and associated 95% Clopper-Pearson confidence interval, and in Part 2, the difference in the percentage between those who received INO-4700 and their corresponding same regimen placebo together with associated 95% confidence interval. Related SAEs and related Grade 3 or higher AEs will also be analyzed as described above within and between associated placebo in part 1. The frequencies will also be presented separately by dose number and will be depicted by system order class and preferred term. Additional frequencies will be presented with respect to maximum severity and relationship to IP. Multiple occurrences of the same AE in a single subject will be counted only once following a worst-case approach with respect to severity and relationship to IP. All serious TEAEs will also be summarized as above. AE duration will be calculated as AE stop date – AE start date + 1 day. AEs and SAEs that are not TEAEs or serious TEAEs will be presented in listings.

All of these primary safety analyses will be conducted on the participants in the safety population.

8.5.2 PRIMARY IMMUNOGENICITY ANALYSES

For both Part 1 and Part 2, antigen specific binding antibody titers, MERS-CoV neutralizing antibody titers, and specific cellular immune responses will be analyzed by Study Group. Binding antibody titer will be analyzed for each Study Group using the geometric mean and associated 95% confidence intervals. Percent neutralizing antibodies and antigen specific cellular immune response increases will be analyzed for each Study Group using medians, inter-quartile range and 95% confidence intervals. Percentage with overall immune response, inclusive of seroconversion (i.e., positive titer), and corresponding 95% Clopper-Pearson confidence intervals will be analyzed within each Study Group.

In Part 1, the difference in percentage of overall immune responders including seroconverters between all pairs of INO-4700 Study Groups will be calculated along with corresponding exact 95% confidence intervals.

In Part 2, the primary hypothesis of H0: $p \leq 70\%$ versus H1: $p > 70\%$ will be tested with an exact test of a binomial proportion. In addition, the binding antibody titer difference between INO-4700 and placebo will be analyzed using the geometric mean fold ratio and associated 95% confidence interval. Percent neutralizing antibodies and antigen specific cellular immune response differences between INO-4700 and placebo will be analyzed using the difference in medians and associated 95% confidence intervals.

All of these primary immunogenicity analyses will be conducted on the participants in the mITT and PP populations.

8.5.3 SAFETY ANALYSES

Laboratory response variables will be descriptively summarized in accordance with time point and as changes from baseline including 95% confidence intervals. Laboratory values considered clinically significant will be presented in listings for participants in the safety population.

Measurements for vital signs as well as changes from baseline will be descriptively summarized by time point for participants in the safety population.

Serum pregnancy at Screening and urine pregnancy at each post baseline time point will be descriptively summarized for participants in the safety population.

The percentage of participants with abnormal medical history findings will be summarized by body system and preferred term for participants in the safety and mITT populations.

For statistical analysis purposes, prior medications are defined as those that were used and stopped before the start of the trial (prior to Day 0) and concomitant medications are defined as those used during the course of trial (on or after Day 0). Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. Data for all prior and concomitant medications will be summarized with percentages for participants in the safety and mITT populations.

8.5.4 DISPOSITION

Subject disposition will be summarized for all randomized participants and will include the number and percentage randomized, the number and percentage who received each planned dose and the number who completed each part of the trial. The number and percentage of participants who discontinued IP in each part of the trial 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

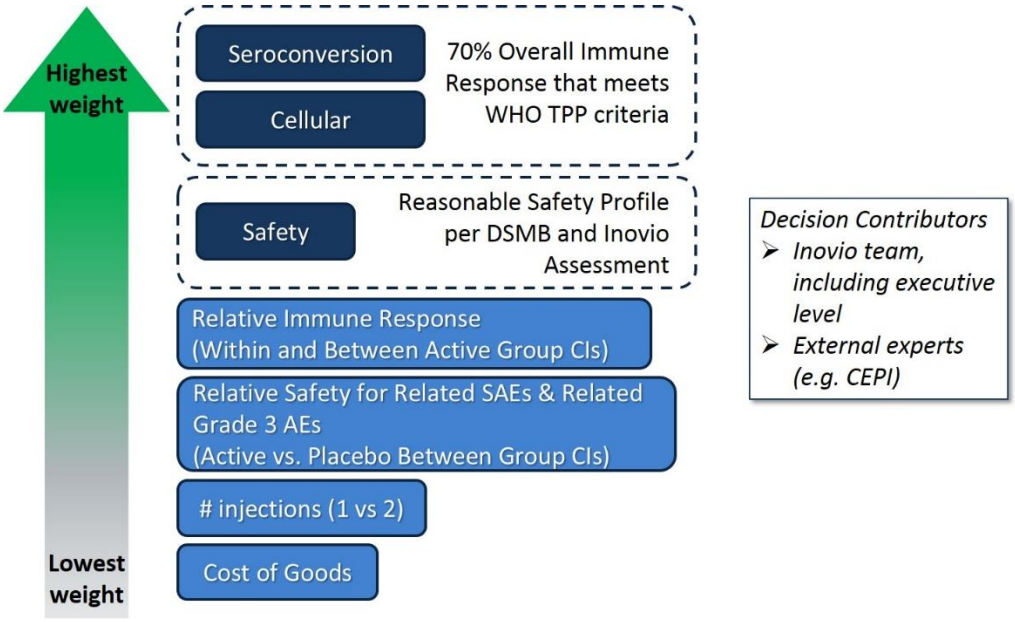
Demographic and baseline characteristic data will be descriptively summarized for participants in the safety and mITT populations.

8.5.6 INTERIM ANALYSES

No formal interim analyses will be performed for this trial. However, safety and tolerability will be assessed by the DSMB as noted above for the participants in each Study Group.

A Sponsor unblinded review of the week 10 immunogenicity and safety data will be made during Part 1 of this study when all evaluable data observations are available in order to determine the optimal dose for the Part 2 of the study. The selection of the optimal dose for Part 2 will involve consideration of weighted ordered criteria described in Figure 3 below.

Figure 3: Weighted Ordered Dose Selection Criteria



At a minimum, the optimal selected dose will have a 70% overall immune response and acceptable safety profile as determined by the DSMB and Inovio Medical Council. Other criteria listed in Figure 3 will contribute to the selection of the right optimal dose if the overall immune responses and safety profiles are similar between the Study Groups in Part 1.

A group-level unblinded review of the immunogenicity and safety data will be made once week 12 visit data are complete for all participants in Part 2 whilst maintaining subject-level blinding. Long-term follow-up data will continue to be collected for all participants with remaining visits through to the final visit. These summaries and analyses will allow the Sponsor and collaborators to have results with respect to the immunogenicity and safety endpoints up to and including the Part 2 Week 12 visit on which to inform product development goals. 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. Thus, Part 2 of the trial will remain blinded to the Sponsor and collaborators with respect to subject treatment assignment.

In order to protect the blind, for the group-level unblinded review, no safety analysis will be provided if the total of subjects who experience the event of interest is greater than 0

and the count of these events relative to the total count of events produces a percentage less than 3% for a given analysis.

8.5.7 MULTIPLICITY

No adjustment for multiplicity will be made for this trial.

8.5.8 MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be done on reported values.

8.5.9 EXPLORATORY ANALYSES

T and B post baseline cell number will be analyzed descriptively by Study Group using the mean or median and associated 95% confidence intervals.

In Part 2, treatment difference comparisons will include a comparison of two dose INO-4700 participants who are boosted with INO-4700 versus two dose INO-4700 participants who are boosted with placebo.

Exploratory ANCOVA and Logistic models may be fit that include baseline, confounder variables such as age, antibodies to other coronaviruses and gender to test the relationship between study group and different immune response variables. The relationship between antibodies to other coronaviruses and humoral immune responses will be explored using regression methods such as linear regression.

8.6 SAMPLE SIZE/POWER

No formal power analysis is applicable to Part 1 of this trial, as descriptive statistics will be used to summarize the data.

For each Study Group in Part 1 of the trial with 32 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <11% if no SAEs are observed in a study group. For all the Study Groups combined in Part 1 of the trial with 160 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <3% if no SAEs are observed in this study phase. For all Study Groups combined across Parts 1 & 2 of the trial with 460 INO-4700 administered participants, the study provides 95% confidence that the true incidence of SAEs is <1% if no SAEs are observed.

For Part 2 of this trial, an evaluable sample of 260 active subjects treated with INO-4700, which will be used for formal hypothesis testing, provides >90% power to detect an INO-4700 overall immunological response rate of 70% or higher should this overall response rate truly be 80%, using a one-sided type 1 error rate of 0.025.

8.7 RANDOMIZATION AND BLINDING

Part 1 of this study will be randomized across Study Groups (A through I). Part 2 of this study will be randomized between the selected optimal Active dose from Part 1 and placebo groups. The study is Investigator-and-participant blinded except for the site pharmacy across all Study Groups for both parts of the study. The Sponsor will be blinded in Part 1 until Week 10 and blinded for the entire duration of Part 2 of the study.

For the Part 2 Week 12 analysis, group level unblinded summaries of immunogenicity and safety will be produced. The Sponsor will continue to remain blinded to subject-level treatment allocation for the remainder of the trial.

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 participant 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

<u>Institutional Biosafety Committee (IBC), if applicable</u>

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 PARTICIPANTS

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

Participants are not required to follow special instructions specific to the IP used in this clinical trial. Participants will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should 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 participants, 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 participants 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

This clinical trial will utilize an eSource system. In most cases, sites will document source data directly in eSource. However, there will be circumstances where source data will exist in paper records, (e.g. laboratory reports, informed consent and previous medical history records.

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. Participants must not be identified by name on any CRFs. Participants 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 Medical Monitor will regularly review safety and tolerability data throughout the trial in a blinded fashion until unblinding. Additional safety reviews will be conducted by a DSMB, and they will be responsible for reviewing all unblinded safety data, including AEs of clinical significance, AESIs and SAEs, as well as safety laboratory data. Safety reviews will include data from all enrolled participants.

The DSMB is not blinded to IP allocation and will review unblinded safety data. The DSMB will be charged with advising whether there appears to be any safety concerns and to make recommendations regarding continued enrollment, trial pause and trial suspension. If the safety data is considered unsatisfactory during any safety review, the study may be paused or stopped. In this case, further enrollment and administration of INO-4700 or placebo to participants will be paused for further evaluation. The Sponsor will perform an investigation and consult the DSMB and other experts, if needed, to determine whether to resume randomization and/or dosing of the remainder of the participants. For further details see 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. Records for all clinical trial participants in this clinical trial will be monitored. The following clinical trial site monitoring tasks will be performed at all clinical trial sites:

- Prior to subject screening at the site, a Site Initiation Visit will be conducted to review all relevant forms and documentation, and ensure that the clinical trial site staff are qualified and compliant with all applicable requirements
- All clinical trial site monitoring visits will be documented
- Periodic clinical trial site visits will be performed throughout the clinical trial
- The blinded 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 SAE and provide subsequent follow-up report of the final outcome to the IRB.

- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities 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 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.

- The unblinded 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 while maintaining the blind and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor while maintaining the blind.
  - Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
  - Assure that the pharmacy continues to be acceptable.
  - Assure that investigational drug accountability and reconciliation of records are complete and accurate.

13.0 FINANCING AND INSURANCE

Inovio Pharmaceuticals is the Sponsor and is fully supporting the study with funding provided by the Coalition for Epidemic Preparedness Innovations (CEPI). 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, ICH E6 and/or local regulations, where applicable.

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	Attributable, Legible, Contemporaneous, Original, and Accurate
bGH polyA	Bovine growth hormone 3' end poly-adenylation signal
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
CEPI	Coalition for Epidemic Preparedness Innovations
Cl	Chloride
CO_2	Carbon Dioxide
Cr	Creatinine
CRF	Case Report Form
CS	Clinically Significant
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electroporation
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
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
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
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SID	Subject Identification Number
SOC	System Organ Class
SSC	Saline Sodium Citrate
SynCon	Synthetic consensus
TMF	Trial Master File
UADE	Unanticipated Adverse Device Effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

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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 MERS-CoV vaccine development.

Body System	AESI
Respiratory	Acute respiratory distress syndrome (ARDS)
	Pneumonitis/pneumonia
Neurologic	Generalized convulsion
	Aseptic meningitis
	Guillain-Barré Syndrome (GBS)
	Encephalopathy
	Encephalitis
	Myelitis
	Acute disseminated encephalomyelitis (ADEM)
	CNS vasculopathy (stroke)
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation (DIC)
Immunologic	Anaphylaxis
	Vasculitides
	Enhanced disease following immunization
Other	Local/systemic SAEs (regulatory criteria)
	Acute renal failure
	COVID-19
	Death, including maternal death, spontaneous abortion, stillbirth and neonatal death

Signature Page for VV-TMF-00167 v2.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 12-Feb-2021 20:37:28 GMT+0000

Signature Page for VV-TMF-00167 v2.0

Protocol Administrative Memo (PAM) # 1.0
PAM Date: 12Oct2020

To

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Version: 1.0

Protocol Version Date: 23Mar2020

Sponsored by:

Inovio Pharmaceuticals, Inc.

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted], M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc

Date (ddMmmyyyy)

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

The Principal Investigator's (PI's) signature constitutes the PI's acknowledgement of, and agreement with, this PAM 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 (first and last)

_____ _____

Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Administrative Change to Tables 4, 5 and 6

- Administrative change to Table 4, footnote "o," Table 5, footnote "l," and Table 6, footnote "l."

Each footnote indicates "4 x 8.5 mL (34 mL) whole blood in 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 (screening and prior to Day 0 dosing)."

The footnotes should indicate 4 x 8 mL (approximately 32 mL) whole blood in 8 mL Cell Preparation Tubes (CPT) per time point. Note: Collect a total of 64 mL whole blood prior to 1st dose (screening and prior to Day 0 dosing)."

Item 2: Typographical Error in Tables 5 and 6

- Typographical Error in Tables 5 and 6, Screening Visit Procedures.

Tables 5 and 6 indicate an "X" under "Screening" for "INO-4700 or placebo + EP" in error. As indicated throughout the protocol, investigational product is not administered until Day 0.

Item 3: Change in Safety Contact Information, Section 7.9

- The phone, fax and email address for safety reporting have been updated.

All references to the safety reporting contact information will be updated as follows:

	In Protocol V1.0	Updated Information
Sponsor Safety Email	safety@inovio.com	safety.inovio@apcerls.com
Sponsor Safety Fax	[redacted]	[redacted]
Sponsor Safety Phone	[redacted]	[redacted]

Sites are to use the updated information only.

Signature Page for VV-TMF-43494 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 15-Oct-2020 13:56:57 GMT+0000

Signature Page for VV-TMF-43494 v1.0

Protocol Administrative Memo (PAM) # 2.0
PAM Date: 16Nov2020

To

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Version: 1.0

Protocol Version Date: 23Mar2020

Sponsored by:

Inovio Pharmaceuticals, Inc.

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted], M.D., Ph.D.
[redacted]
Inovio Pharmaceuticals, Inc

Date (ddMmmyyyy)

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

The Principal Investigator's (PI's) signature constitutes the PI's acknowledgement of, and agreement with, this PAM 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 (first and last)

_____ _____
Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Change in Medical Monitor

Note that effective 19Nov2020, [redacted] MD, FACP, FIDSA will assume Medical Monitor responsibilities for this trial.

- Safety Contact Information, Section 7.9, Table 9: The updated Medical Monitor contact information is as follows:

Table 9: Medical Monitor Direct contact Information

Medical Monitor: [redacted] MD, FACP, FIDSA
Email: [redacted]
Cell Phone: [redacted]

Sites are to use the updated information only.

Signature Page for VV-TMF-47665 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 18-Nov-2020 12:42:32 GMT+0000

Signature Page for VV-TMF-47665 v1.0

Protocol Administrative Memo (PAM) # 3.0
PAM Date: 29Jan2021

To

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Version: 1.0

Protocol Version Date: 23Mar2020

Sponsored by:

Inovio Pharmaceuticals, Inc.

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted] MD, FACP, FIDSA
[redacted]
Inovio Pharmaceuticals, Inc

Date (ddMmmyyyy)

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

The Principal Investigator's (PI's) signature constitutes the PI's acknowledgement of, and agreement with, this PAM 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 (first and last)

_____ _____

Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Change in Medical Monitor

Note that effective 01Feb2021, [redacted], MD will assume Medical Monitor responsibilities for this trial.

- Safety Contact Information, Section 7.9, Table 9: The updated Medical Monitor contact information is as follows:

Table 9: Medical Monitor Direct contact Information

Medical Monitor: [redacted], MD
Email: [redacted]
Phone: [redacted]

Sites are to use the updated information only, beginning 01Feb2021.

Signature Page for VV-TMF-50511 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 29-Jan-2021 17:13:57 GMT+0000

Signature Page for VV-TMF-50511 v1.0

Protocol Administrative Memo (PAM) # 4.0
PAM Date: 15Mar2021

To

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Healthy Volunteers

Protocol Version: 1.0

Protocol Version Date: 23Mar2020

Sponsored by:

Inovio Pharmaceuticals, Inc.

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted], MD

[redacted]

Inovio Pharmaceuticals, Inc

Date (ddMmmyyyy)

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

The Principal Investigator's (PI's) signature constitutes the PI's acknowledgement of, and agreement with, this PAM 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 (first and last)

_____ _____
Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Serum Chemistry - Bicarbonate Value

Per Protocol Version 1.0, bicarbonate will be reported as HCO_3. However, some sites are set-up to report bicarbonate as CO_2. As the function of this test is supported by reporting as either HCO_3 or CO_2, using either is acceptable.

- Table 4, Table 5, Table 6, Section 6.1.1 and Section 6.4: Bicarbonate [HCO_3] should be Bicarbonate [HCO_3 or CO_2].

Protocol Version 2.0 allows for reporting using either HCO_3 or CO_2.

Signature Page for VV-TMF-52150 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 16-Mar-2021 15:16:08 GMT+0000

Signature Page for VV-TMF-52150 v1.0

Protocol Administrative Memo (PAM) # 5.0
PAM Date: 20Jan2023

To

MERS-201

Study to Evaluate the Safety, Tolerability and Immunogenicity of INO-4700 for Middle East Respiratory Syndrome Coronavirus (MERS-Co) in Healthy Volunteers

Protocol Version: 2.0

Protocol Version Date: 12Feb2021

Sponsored by:

Inovio Pharmaceuticals, Inc.

Medical Monitor Approval Page

Medical Monitor Signature:

[redacted], MD
[redacted]
Inovio Pharmaceuticals, Inc

Date (ddMmmyyyy)

This memo contains information that is considered to be administrative or clarifying in nature and does not meet the criteria of an immediate protocol amendment. Please distribute this memo to all appropriate staff members, and file it with the site's protocol documents. Consult the local Institutional Review Board (IRB)/ Research Ethics Board (REB)/Ethics Committee (EC) regarding submission requirements for Protocol Administrative Memos (PAMs).

Principal Investigator Acknowledgement

I have read and understood this Protocol Administrative Memo (PAM) and will incorporate it as part of the Protocol. I will submit this PAM, if required, to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) overseeing the conduct of the clinical trial in accordance with their policies and procedures and local requirements.

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

Principal Investigator Signature:

_____

Principal Investigator Printed Name (first and last)

_____ _____

Principal Investigator Signature Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

Item 1: Discontinuation of Study into Part 2 and Analysis of Week 48 Samples

The MERS-201 trial will not proceed to Part 2. The decision was made in collaboration between the Study Sponsor, Inovio Pharmaceuticals, Inc. (INOVIO) and the Study Funder, The Coalition for Epidemic Preparedness Innovations (CEPI). The decision was based on the Week 10 interim immunology results, which did not meet the criteria for Part 2 dose selection as outlined in the Protocol Section 8.5.6, for any dose group in Part 1. There were no safety concerns related to the study and Week 10 interim safety results were consistent with the safety results across Inovio's platform for intradermal administration.

Since the study objectives were not met and the study is not moving forward into Part 2, no additional immunology data is needed. Therefore, the Part 1 Week 48 samples will not be analyzed.

Signature Page for VV-TMF-131691 v1.0

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 20-Jan-2023 21:27:47 GMT+0000

Signature Page for VV-TMF-131691 v1.0