CORVax12 - a phase I trial of SARS-CoV-2 spike (S) protein plasmid DNA vaccine (CORVax) +/- pIL-12 (tavokinogene telseplasmid) in healthy volunteers, with immunodynamic biomarker monitoring of coordinated cellular/humoral response.

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PROTOCOL SIGNATURE PAGE

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I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Federal Regulations, Good Clinical Practices, and local regulatory requirements.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist regarding the study agent(s) and the conduct of the study.

Rom Leidner, MD		9/29/2020
Investigator Name (print)	**Investigator Signature**	**Date**

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Investigator Name (print)	**Investigator Signature**	**Date**

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1. RATIONALE

DNA vaccines have been widely explored and remain a promising immunotherapeutic strategy suitable for infectious diseases. DNA vaccines could represent an affordable, safe and effective alternative to conventional vaccines. Plasmid DNA-based vaccines are considerably faster and easier to manufacture than most other vaccine platforms. Further, DNA-encodable prophylactic vaccines with electroporation represent a safe and effective approach to initiate both humoral and cellular immunity in healthy volunteers directed at a variety of infectious diseases, including coronavirus.

The choice of immunogen for a DNA-encodable coronaviral vaccine is critical for not only the magnitude but also quality of immune response. The coronavirus spike (S) protein is composed of two subunits; the S1 subunit contains a receptor-binding domain that engages with the host cell receptor angiotensin-converting enzyme 2 (ACE2) and the S2 subunit allows viral-cell membrane fusion. Collectively, the S protein has been shown to induce long-term and potent neutralizing antibodies and/or protective immunity in various preclinical severe acute respiratory syndrome (SARS)-CoV studies and in both preclinical and clinical studies in Middle East Respiratory Syndrome (MERS)-CoV studies. These previous vaccine studies, which were based on the spike protein from different strains of coronavirus, provide an immunological framework for this vaccine concept.

While the immunological data from these related (S) protein vaccines are foundational for our SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccine, there remains a possibility that targeting a frequently mutated viral sequence with the potential for antigenic drift may limit the efficacy of this approach. However, genetic alignments of multiple reported SARS-CoV-2 strains point to a relatively conserved sequence even among the recently described 3 clades[1,2]. The S protein construct used in this proposal originated in Dr. Barney Graham's Viral Pathogenesis Laboratory at the NIH (National Institute of Allergy and Infectious Diseases) and represents a highly conserved consensus sequence based on the first reported SARS-CoV-2 sequences. Further, our group evaluated approximately one hundred DNA sequences of SARS-CoV-2 cases in the USA that were downloaded from GISAID (Global Initiative on Sharing All Influenza Data, gisaid.org – accessed March 16, 2020). All sequences of the 'S' gene, coding for spike (S) glycoprotein, were aligned to reference gene ID 43740568 (NC_045512.2 bases 21563-25384). Multi-sequence alignment of these ~100 gene sequences resulted in no alignment gaps (i.e., no indels or significant structural alterations). The aligned DNA sequences were translated to amino acids and evaluated for percent identity to the reference protein sequence. All positions of spike (S) glycoprotein had 100% identity to reference with the exception of amino acids H49 (99%), F157 (99%), G181 (99%), V483 (96%), D614 (97%), and H655 (99%). Notably, V483 is in the receptor-binding domain (RBD) to angiotensin-converting enzyme 2 (ACE2); however, this position is not a contact residue, it is merely an alanine substitution, and is of low conservation among homologous coronavirus strains.

Interleukin 12 (IL-12) plays an integral role in the induction of a Th1-biased response while coordinating both the innate and adaptive immune systems. Besides triggering cellular immunity, IL-12 can also augment antigenicity via activation of antigen presenting cells as well as assist the humoral response by encouraging isotype switching towards a more functional antibody. With the inclusion of IL-12, the proposed vaccination (CORVax12) is designed to drive a coordinated immune response, capable of drawing upon the innate, adaptive humoral, and adaptive cellular arms. This multi-pronged immunity is likely to be important at generating robust anti-viral responses as previous studies with SARS-CoV identified a critical role for each component.

Based on these data we consider that vaccination with the proposed SARS-CoV-2 (S) protein plasmid provides an opportunity to evaluate whether vaccination alone or combined with IL-12 is safe, provides a strong neutralizing Ab response to the virus, and induces a T cell response to viral antigens.

2. BACKGROUND

Coronaviruses, which can infect and cause disease in both mammals and birds, typically lead to mild respiratory infections such as the common cold. However, although rare, coronavirus strains such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) can be lethal.

On December 31, 2019, a novel strain of coronavirus, coined SARS-CoV-2 by the World Health Organization (illness from SARS-CoV-2 is COVID-19), was discovered after tracing the origins of a pneumonia outbreak in Wuhan, China. SARS-CoV-2 identifies as a novel strain of betacoronavirus that is capable of person-to-person spread[3]. Previous international emergency betacoronavirus outbreaks include both the genetically similar SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome)[4].

The World Health Organization has determined the COVID-19 outbreak to be a global pandemic. To combat the rapid spread of the virus, governments across the world, including the United States, have taken steps to limit spread, including travel restrictions, sheltering in place, and quarantines. Because coronaviruses typically present with symptoms mirroring the common cold, there has historically been a low interest in developing an antiviral. However, with the progression of the current pandemic, the need to develop vaccines that can help contain these viruses has become clear.

As further described below, Drs. Leidner, Fox, and colleagues have worked with researchers at OncoSec Medical Incorporated (OncoSec) to develop a novel vaccine approach for COVID-19. The plan is to employ OncoSec's proprietary gene delivery system, using established electroporation technology to deliver a plasmid-based DNA vaccine encoding the SARS-CoV-2 spike (S) glycoprotein together with a plasmid encoding IL-12p70.

Here, we describe both a novel DNA-encodable vaccine approach which includes the use of the IGEA CLINIPORATOR® - Model EPS02 ("CLINIPORATOR") generator, which provides a favorable transfection profile. The CLINIPORATOR® generator achieves its high transfection efficiency by using a lower voltage with longer duration pulses, which, based on preclinical evaluation of OncoSec's generator (with identical electroporation parameters), have resulted in improved expression of the electroporated genes.

Vaccination with Electroporation (EP): Its Mechanism and Advantages

DNA vaccines can be delivered with viral and bacterial vectors but are often limited by poor transfection rates and/or rapid clearance by neutralizing antibodies [5,6]. Alternative methods of delivering DNA vaccines, such as electroporation, continue to be explored. Electroporation (EP) is a technique that applies electric pulses to transiently permeabilize a cell membrane, thereby promoting uptake of macromolecules such as nucleic acids into the cell. *In vivo* EP has been used in many clinical trials to deliver DNA vaccines and drugs to various tissues[7]. Importantly, it has been shown to dramatically improve gene delivery (100-1000-fold), which is foundational to the immunogenicity of DNA vaccines[8,9].

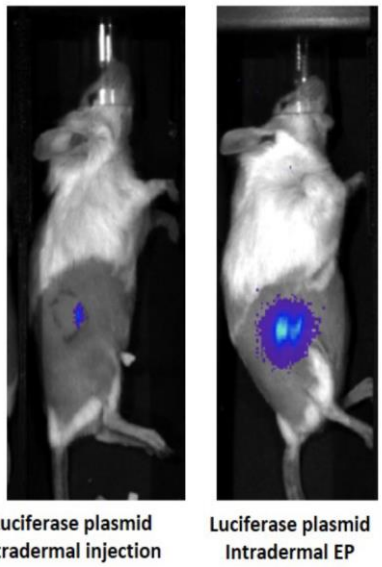


Figure 1. Expression of luciferase 48 hrs following intradermal injection and electroporation of luciferase plasmid.

The location and cellular architecture of the tissue into which DNA vaccines are delivered can modulate the effectiveness and/or type of immune response that is generated. EP-mediated delivery targeting the skin has been attracting considerable attention[10]. Skin is the most accessible organ and, in part due to an abundance of antigen presenting cells (APC) such as Langerhans cells and skin-resident dendritic cells, is highly efficient at presenting antigens and priming an effective cellular (T cell-mediated) anti-viral response[10,11]. With the use of the CLINIPORATOR® electroporation device, we will target the skin, as it has been successfully transfected using low-voltage parameters with a DNA-based reporter protein (**Fig.1**) and has lower levels of pain and toxicity

This clinical trial will evaluate the safety and anti-viral immune stimulating efficacy of combining electroporation of plasmid encoding both the coronavirus spike (S) glycoprotein and IL-12. IL-12 is a proinflammatory cytokine known to efficiently support NK and macrophage function as well as to polarize a Th1-biased T cell response. Previous viral studies have demonstrated an increase in both cellular and humoral immune responses upon delivery of DNA-encodable IL-12 via electroporation[12]. Additionally, control of the SIV/HIV infection correlated strongly with the IL-12-mediated increase of SIV-specific CD8+ and CD4+ T cells[13]. Together, a strong rationale is evident for combination immunotherapy including plasmids encoding both the SARS-CoV-2 (S) protein and IL-12 (together, CORVax12). The IL-12 plasmid employed in this study has been used as intratumoral treatment in eight clinical trials with evidence of increased immune infiltrates and anticancer effects.

Combination of IL-12 with a Vaccine Directed Against SARS-CoV-2 Spike (S) Glycoprotein

Currently, little is known about the mechanisms of transmission, infection, and immunity related to SARS-CoV-2. However, phylogenetic analyses have revealed that of all the viral strains from the family Coronaviridae, SARS-CoV-

2 shares the greatest similarity with the severe acute respiratory syndrome (SARS) strain[1,14]. In fact, three strains of SARS-CoV-2 together with two bat-derived SARS-like strains, form a distinct clade of coronaviruses [3].

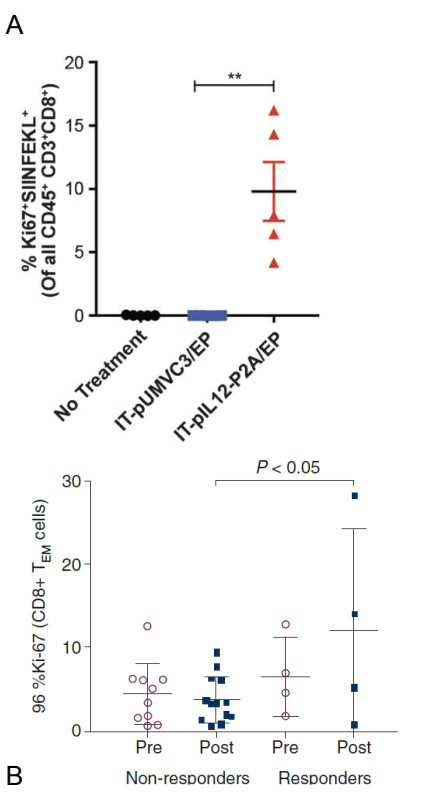


Figure 2: (a) electroporation of plasmid IL-12 generates proliferating, antigen-specific splenocytes by day 7 (b) Increased frequency of proliferating memory CD8⁺T cells in the periphery is significantly increased in responders on treatment

The antigenic foundation of this prophylactic vaccine, SARS-CoV-2's spike (S) glycoprotein, was selected based on demonstrated immunogenicity (both cellular and humoral), as well as previously having been identified as an appropriate antigen to drive anti-viral responses in other strains of coronavirus including [15–17]SARS and MERS. Further, multiple isolates of SARS-CoV-2 have identified a relatively conserved genetic sequence that codes for the (S) protein with limited synonymous mutations between strains[14,18], which may help to limit immune escape variants seen with other unstable genetic elements. To this point, OncoSec has secured and will use the augmented DNA-encodable spike protein developed in Dr. Barney Graham's laboratory at the NIH[1] as the antigenic component of the vaccine.

OncoSec is a cancer immunotherapy company with extensive experience in delivering therapeutic levels of DNA-encoded IL-12 (interleukin-12 plasmid, tavokinogene telseplasmid) via reversible electroporation. OncoSec has demonstrated that intratumoral electroporation of plasmid IL-12 can prime significant frequencies of proliferating antigen-specific CD8+ T cells in the spleen of treated mice[19] as well as memory subsets in on-treatment responding patients [20] (Fig 2). These and other clinical studies, along with an abundance of historic IL-12 data, support the inclusion of this cytokine in the CORVax12 vaccine platform.

The design of this clinical trial will evaluate whether the addition of IL-12 to the vaccination strategy will augment the adaptive anti-SARS-CoV-2 immune response. While protection against SARS-CoV-2 infection appears to be mediated by neutralizing Ab, cellular immunity has been shown to play a large role in controlling SARS-CoV, with both innate (NK) and adaptive (CD4+ T cells) arms providing critical Th1-directed cytokines such IFN-γ and TNF-α[21,22]. These data underscore the rationale for testing the addition of IL-12, a cytokine that can augment priming of Type 1 T cell responses and augment effector function of T cells and NK cells[23].

Antibody-dependent enhancement (ADE) concerns

The phenomenon of antibody-dependent enhancement (ADE) has been reported for dengue[24], HIV-1[25], and influenza[26]. Wang et al, demonstrated experimentally that monoclonal antibodies to SARS-CoV spike protein resulted in ADE, as did highly diluted anti-sera[27], whereas polyclonal, undiluted anti-sera, neutralized SARS-CoV infection. Inclusion of IL-12 in the vaccine platform under study may further safeguard against ADE, acting as the adjuvant to trigger both the effector CD8⁺ T cell response as well as the complimentary CD4⁺ T cell response which can deepen the humoral response.

Rationale for vaccine route of administration and dose

The rationale for administering plasmid encoding the SARS-CoV-2 (S) protein to the dermis includes several points. We hypothesize that dermal expression of both IL-12 and SARS-CoV-2 (S) protein will result in limited expression within the nearby dermis, leading to antigen presentation in the draining lymph node that, secondary to the influence of IL-12, will result in the priming of an anti-viral immune response that is polarized to a type 1 immunity. By comparing the immune response of subjects receiving SARS-CoV-2 (S) alone with those receiving SARS-CoV-2 (S) plus IL-12, we will be able to test our hypothesis that inclusion of IL-12 will augment the magnitude and breadth of the T and B cell anti-viral response. The rationale for the dose of 0.8 mg into the dermis is based on the relatively small differences in the antibody response of subjects receiving electroporation of plasmid vaccines[12]. Further, a current vaccine study for SARS-CoV-2 is electroporating 1 or 2 mg of plasmid into the dermis. In this study subjects will receive either 0.8 mg of spike protein alone or 0.8 mg of spike protein combined with 0.8 mg of IL-12 plasmid.

Rationale for parallel age cohorts

The mortality and morbidity burden of COVID-19 is overwhelmingly among individuals over the age of 50, yet the convention in early phase vaccine trials has been to test in the 18 to 50 year age bracket. Therefore, we have designed this phase 1 trial to assess the safety profile of this vaccine platform in two age groups: 18 to 50 years, as is convention; but also, and we think importantly, in parallel cohorts from the over 50 age bracket, a decision which is warranted by the extraordinary circumstances of the current pandemic. It will be essential to know that this vaccine is safe in the over 50, at-risk population. Not to do so, could delay safety ascertainment for the target population and hinder detection of early efficacy signals that might otherwise surface for the at-risk demographic, in the event of rebound or seasonal cycling of SARS-CoV-2.

3. OBJECTIVES & SCHEMA

Primary Objective

To determine the safety profile of CORVax +/- pIL-12 in healthy volunteers, age 18-50 or age > 50.

Outcome Measures

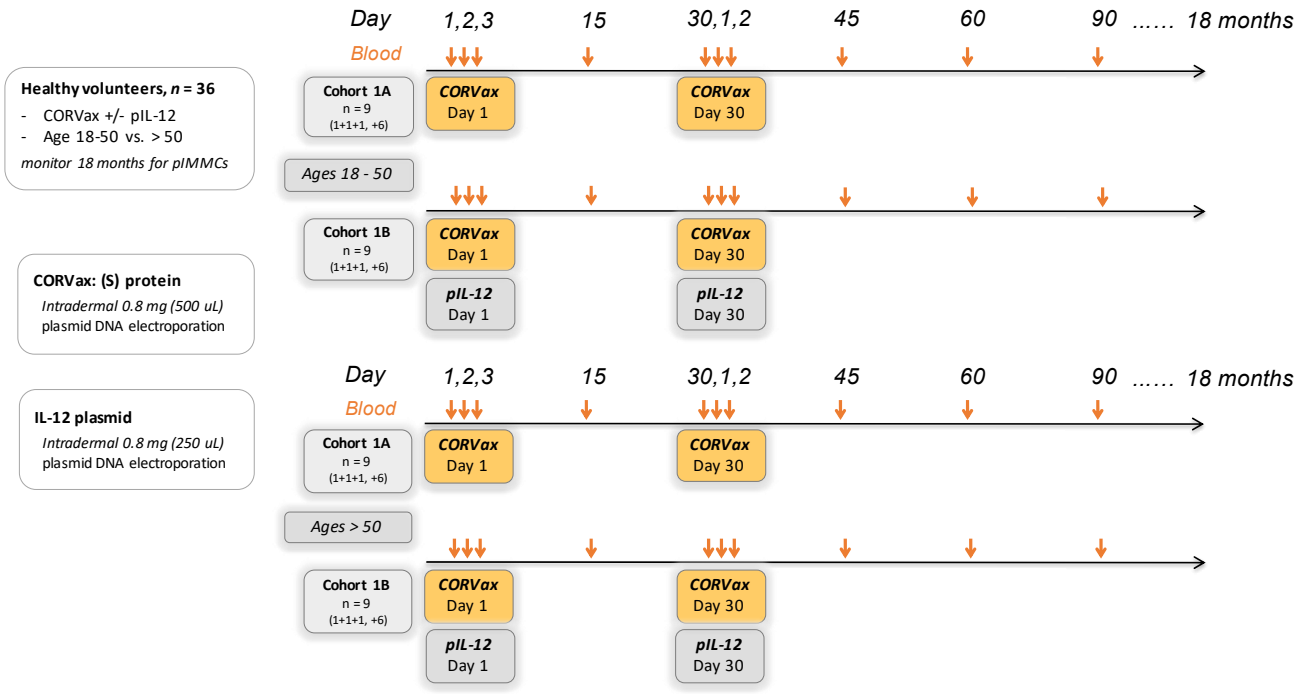
- Toxicity and Adverse Events (AEs) based on FDA Guidance for Industry 2005D-0155: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.
- 90 day monitoring of hematology, serum chemistry, and creatine phosphokinase.
- 90 day monitoring of serial physical exam, vital signs, and durable pain score.
- Extended monitoring of Medically Attended Adverse Events (MAAEs) for potentially immune-mediated conditions (pIMMCs)

Exploratory Objectives

Immunodynamic biomarkers (section 9).

Outcome Measures

- Blood sampling for plasmid expression levels and immune response measurements will occur on days 1, 2, 3, 15, 30, 31, 32, 45, 60 and 90 of study.
- The main objectives of the monitoring will be to characterize both the humoral and cellular immune response to the pUMVC3-CORVax vaccine.



4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Healthy adult volunteers ages 18 years and above, who are able to provide written informed consent and willing to allow storage and future use of samples for SARS-CoV-2 related research.

4.1.2 Women of childbearing potential (WOCBP) must have negative serum or urine pregnancy on each day of vaccine administration.

4.1.3 Males and women of childbearing potential must agree to take appropriate precautions to avoid pregnancy during treatment and through 180 days after last dose of IP.

4.2 Exclusion Criteria

4.2.1 Current or previous SARS-CoV-2 infection or receipt of an experimental treatment for prevention of SARS-CoV-2.

4.2.2 Administration of any vaccine within 4 weeks of first dose.

4.2.3 Any laboratory abnormalities at baseline greater than Grade 1 per the ”FDA 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

4.2.4 Any history of cardiac arrhythmia.

4.2.5 Any history of epilepsy or seizure within the last five years.

4.2.6 Use of immunosuppressive medication within 14 days before the first dose of study drug.

4.2.7 Anticipated treatment with TNF-α inhibitors (e.g., infliximab, adalimumab, or etanercept).

4.2.8 Pregnancy or breastfeeding.

4.2.9 Body mass index of 35 kg/m2 or more.

4.2.10 Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose.

4.2.11 Chronic liver disease or cirrhosis.

4.2.12 Previous major surgery or any radiation therapy within 4 weeks of group assignment.

4.2.13 Any pre-excitation syndromes (e.g., Wolff- Parkinson-White syndrome).

4.2.14 Metal implants within 20cm of the planned site(s) of injection; presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition at the planned site(s) of injection; tattoos covering the injection site area.

4.2.15 Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator.

4.2.16 History of allogeneic organ transplantation.

4.2.17 History of primary immunodeficiency.

4.2.18 Known HIV, hepatitis B virus, or hepatitis C virus infection. Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.

4.2.19 Uncontrolled intercurrent illness, including but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, unstable cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the participant to give written informed consent.

4.2.20 Comorbidities, controlled or otherwise, associated with higher risk for severe COVID-19 illness - because our understanding of the pathogenesis of SARS-CoV-2 continues to evolve, this will be based on most current information available at time of screening regarding risk factors for severe disease, using resources such as those described on the Centers for Disease Control website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html

4.2.21 Subjects at high-risk for SARS-CoV-2 exposure per investigator, including healthcare workers, first responders, and individuals with known exposure to individuals infected with SARS-CoV-2.

4.2.22 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice).

4.2.23 History of autoimmune or inflammatory disorders including but not limited to inflammatory bowel disease (e.g., colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, (see Appendix 2).

4.2.24 Known allergy or hypersensitivity to study drug(s) or compounds of similar biologic composition to the study drug(s), or any of the study drug excipients.

4.2.25 Investigator discretion relating to any condition which might interfere with study requirements.

5. REGISTRATION & CANCELLATION GUIDELINES

Subjects must meet all of the eligibility requirements and undergo all pre-study procedures. Subjects will be randomized 1:1 for enrollment to cohort A or B, within their age group (age 18-50 or > 50). Study Numbers will be assigned at enrollment based on the EACRI Immune Monitoring Laboratory (IML) sample ID nomenclature per order of enrollment. All reports & research specimens, including immune parameters or PK/PD, will be labeled with full subject Study Number.

If a subject enrolls in the study, but does not receive study therapy, the subject's enrollment may be canceled. Reasons for cancellation will be documented in writing. Subjects whose enrollment was canceled before receiving study therapy will be replaced.

6. STUDY DESIGN

6.1 Sentinel / Safety Run-In

This is a Phase 1, open-label study to evaluate the safety profile of CORVax +/- pIL-12, (electroporated SARS-CoV-2 spike (S) protein plasmid DNA vaccine with or without the combination of electroporated IL-12p70 plasmid), given as prime & boost doses, four weeks apart, in healthy volunteers, divided into age groups of 18-50 versus > 50 years old. IL-12p70 plasmid DNA electroporation (tavokinogene telseplasmid) has been extensively studied in over 209 subjects across 11 trials including later stage human cancer trials with more than 1000 administrations. The IGEA CLINIPORATOR® system is approved for clinical use in Europe, but remains investigational in this study.

The known side effects seen after the use of the electrode and the application of the electroporation treatment, included injection site pain, redness, swelling, rash, erythema and slight edema, skin exfoliation may be present in the treatment area. These signs usually disappear completely within a few days. The subject may develop superficial abrasions of the epidermis caused by the electrode. The subject's skin may form a crust on the treated area, followed by scarring. Redness or scaling were observed four weeks after the treatment in some subjects.

Pain and muscle contraction with EGT mode is limited. Superficial local anesthesia with lidocaine could be considered in order to reduce the discomfort during needles penetrations.

There are no other side effects which have been reported with the use of the device.

The device uses the same low voltage parameters that have been used in a pre-clinical setting and has been shown to safely transfect plasmids via intradermal routes of delivery. The SARS-CoV-2 spike (S) protein plasmid DNA vaccine is a novel agent. Because this represents a first-in-human combinatorial approach, an initial 1+1+1 sequential safety run-in will be conducted to cautiously assess for dose limiting toxicity (DLT).

One participant will initially be enrolled to each of four cohorts and monitored over a 7-day DLT window:

1A. Age 18-50; CORVax.
1B. Age 18-50; CORVax + pIL-12.
2A. Age > 50; CORVax.
2B. Age > 50; CORVax + pIL-12.

If after 7 days, no DLT are observed, the cohort may proceed to enroll a second participant. If after monitoring the second participant for 7 days, no DLT are observed, the cohort may proceed to enroll a third participant. If after monitoring the third participant for 7 days, no DLT are observed, the cohort may proceed to enroll six additional participants, for a total of nine participants per cohort using a (1+1+1, +6) design.

6.2 Dose Limiting Toxicity

Toxicity and AE assessment is adapted from the 2005D-0155 FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix 1). Relational attribution of AEs will be determined by the investigator as: definitely/probably/possibly/not related to study treatment; immune-related yes/no; autoimmune definitely/probably/possibly/not; and expected/unexpected.

Any AEs considered as definitely/probably autoimmune, and lasting more than 7 days, will be categorized as unexpected and as a pIMMC (see Appendix 2).

Dose limiting toxicity (DLT) is defined as any Serious Adverse Event (SAE) or a Grade 3 or higher toxicity that in the opinion of the investigator is considered at least possibly related to study treatment.

6.3 Stopping Rules

The safety stopping rules will be applied to terminate a specific study cohort if more than one of the first three participants in the cohort suffers DLT which includes any SAE considered at least possibly related during the initial 7-day sequential DLT run-in (1+1+1); or at any time thereafter, if more than two participants in the cohort experience DLT (1+1+1, +6).

For the day-30 “boost” vaccination, the same 7-day sequential DLT run-in design (1+1+1, +6), and the same safety stopping rules apply.

Study enrollment and dosing will be halted if the following safety events are observed with the vaccination or the electroporation (EP) administration:

- 20% or more of subjects across all cohorts (7 or more subjects) experience the same or similar Grade 3 or higher adverse events assessed as at least possibly related to study treatment.
- Any death or SAE assessed as at least possibly related to study treatment.
- Any newly diagnosed pIMMC assessed as at least possibly related to study treatment.
- Any incidental or incorrect voltage or pulse delivery outside the specifications outlined in the User Manual

In the event study halting rules are triggered, the study's safety committee will review all available safety information, and determine whether enrollment and dosing are reasonably safe to continue for either or both vaccine formulations. The safety committee is comprised of three physicians with expertise in immunology who are not investigators on the study: Dr. Brendan Curti, Dr. Matthew Taylor, and Dr. David Page. The committee's review and determination will be documented and submitted to the IRB and FDA.

6.4 Dose Delays

Treatment delay will be allowed for subjects with fever or other signs of an active infection on the day of planned vaccine administration, to include any evidence of infection upon evaluation of the administration sites. Treatment delay should continue until > 48 hours resolution of fever or other signs of active infection. In the event a subject reports symptoms consistent with COVID-19 or known exposure in the interval between 1st and 2nd vaccination, treatment delay is indicated until repeat COVID-19 qPCR is confirmed as negative, before proceeding with study treatment.

6.5 Subject Discontinuation & Replacement

In the event of a positive COVID-19 qPCR test result during the interval between 1st and 2nd vaccination, subject will discontinue study treatment and may be replaced. In the event of treatment delay exceeding 21 days, and absent DLT, subject will discontinue study treatment and may be replaced. In the event of a confirmed positive serum or urine pregnancy test, between 1st and 2nd vaccination, subject will discontinue study treatment and may be replaced. And otherwise, subjects who enroll in the study, and do not complete study treatment for reasons other than DLT, may be replaced.

Discontinuation for the following reasons does not allow for subject replacement: an SAE assessed as definitely/probably related to the investigational product; any Grade 3 or higher unsolicited AE, assessed as definitely/probably related to the investigational product; a new medical condition that would qualify for study exclusion; suspicion or diagnosis of pIMMC, as per section 6.1.

7. STUDY CALENDAR

Schedule of Events	Screen Day -9 to 1	Day 1	Day 2,3	Day 15	Day 30	Day 31,32	Day 45	Day 60	Day 90
Window (days)				+/-1	+/-1	+/-1	+/-1	+/-2	+/-2
Informed consent	X								
Medical history, EKG[1]	X								
Microbiome specimens[2]	X								
NGS whole genome[2]	X								
HIV, HBV, HCV serology[2]	X								
Physical exam	X				X				X
COVID-19 qPCR & serology[2,3,8]	X				X[3,8]			X	X[8]
CMP, CPK, CBC w/ diff	X	X	X	X	X	X	X	X	X
UA and sediment	X	X	X	X	X	X	X	X	X
Immune parameters[2]		X	X	X	X	X	X	X	X
b-HCG[4]		X			X				
Vital signs[5]		X		X	X		X		
CORVax[6] (*intradermal*)		X			X				
pIL-12[6] (*intradermal*)		Cohorts *1B, 2B*			Cohorts *1B, 2B*				
Adverse events[7]		X		X	MAAEs[8]		X	MAAEs[8]	MAAEs[8]
Concomitant medications[9]	X	X	X	X	X	X	X	X	X

1. Electrocardiograms (EKG) to include: heart rate (beats/min), PR interval (ms), QRS interval (ms), RR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes/no), and overall evaluation (normal/abnormal).
2. Refer to Lab Manual; microbiome specimens may be collected at any time up until start of study treatment. Refer to Lab Manual; 50mL whole blood in heparinized tubes (green top) and 5mL serum in SST tube; always collect pre-treatment on relevant study days; collect double baseline set on Day 1 of study.
3. COVID-19 testing should be repeated at any time prior to 2nd vaccination if report of symptoms consistent with COVID-19 or known exposure. This will be performed using the Roche cobas® SARS-CoV-2 qPCR nasal swab and DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG serology platforms, (or updated institutional standard, at time of testing).
4. Serum or urine b-HCG (for WOCBP only) confirmed negative result on the day of vaccine administration.
5. Height at initial visit only; other vital signs at every indicated time point.
6. Refer to Procedure Manual for detailed administration instructions; monitor participants 1 hour post-treatment with vital signs q30 minutes x2, starting 10-15 minutes post vaccination; vitals review by study investigator required prior to release from clinic.
7. Adverse events/toxicity daily query by use of diary or RN/CRC phone call for seven days following each vaccination, including but not limited to injection site pain, redness, swelling, fatigue, headache, nausea, vomiting, diarrhea, myalgia, arthralgia, rash, new pain, dyspnea and temperature (see Appendix 1: Toxicity Grading). Subjects utilizing the diary for AE collection will be called on Day 7 by RN/CRC to review diary entries. On days 1, 15, 30, 45 where vital signs are indicated, AE assessment should be conducted in person by RN, or other PI designee.
8. Monitor for MAAEs at months 1, 2, 3, 6, 12 and 18 with contact by research RN or research associate for potentially immune-mediated medical conditions (see Appendix 2: MAAEs/pIMMCs); repeat COVID-19 qPCR and antibody testing to be performed at any time during the 18 months safety monitoring in the event of potential exposure to SARS-CoV-2 (i.e., close contact tests positive for SARSCoV-2) or symptoms of SARS-CoV-2 infection, with full immunodynamic profiling (section 9) to be performed at the same time. In addition, voluntary extended immune monitoring under longitudinal research specimen protocol, will be offered to all study subjects at day 90.
9. Concomitant medications (including those administered prophylactically) will be collected from 30 days prior to Day 1 through Day 90. In addition, all medications associated with SAEs, MAAEs (including pIMMCs) will be collected through 18 months.

8. ADMINISTRATION OF STUDY TREATMENTS

8.1 Accountability and Compliance of Investigational Product

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. The Investigational Pharmacist will manage drug accountability records. The Investigator or pharmacist/designee may dispense study medication(s) and device components for only subjects enrolled in the study. Individual subject accountability records must be kept by the site staff. The subject number, the date, batch number/wallet number, and quantity of study medication used or returned by the subject, as well as device and device components will be recorded on the appropriate accountability forms by the site staff. These records and the inventory of study medication, device and device components on site will be verified by the study monitor for accuracy and completeness on an ongoing basis throughout the study. Unused drug supplies will be disposed of as instructed in the Study Pharmacy Manual.

Treatment compliance will be assessed at all visits during the study. It will be based on accountability records and an inventory of used/unused supplies. All Investigational Drug Product should be retained at the study site appropriately. At the end of the study, the monitor will conduct a final drug reconciliation for all subjects and the study site overall. All records of study medication administration, accountability records and drug disposition records will be examined and reconciled by the study monitor. Only upon the site monitor completing final drug reconciliation at the site will your monitor authorize the destruction of the unused Investigational Drug Product as directed by UbiVac, OncoSec and the institutional requirements.

8.2 CORVax (SARS-CoV-2 (S) protein plasmid DNA vaccine)

How Supplied
CORVax is formulated in phosphate buffered saline (PBS) for *intradermal* injection followed by *in vivo* electroporation. GLP-grade CORVax is manufactured by UbiVac and available batches will be supplied in labeled 1.5 mL screw top cryovials at a concentration of 1.67 mg/mL and fill volume of 0.7 mL

Storage
CORVax will be stored in separate freezer boxes in a monitored -20°C ±10 freezer. Unopened drug product sterile vials should be stored in the packaging received from UbiVac in a secure, continuously temperature monitored and alarmed freezer in the pharmacy or other appropriate secure location at a nominal temperature of -20ºC. Temperature variation is allowed to a maximum temperature of -10°C. Any temperature excursions greater (warmer) than -10°C must be reported to the Providence Medical Monitor. Drug product which experiences a temperature warmer than -10°C remains suitable for clinical use provided all three of the following conditions are met:

- Maximum one temperature excursion event to temperature greater (warmer) than -10°C.
- Duration of the temperature excursion is not more than 3 hours.
- Maximum temperature achieved is not more than 5°C.

Drug product which experiences temperature excursions outside of these parameters should be immediately quarantined and reported to any member of the Providence Clinical team. Providence (clinical team) will determine whether the affected product remains suitable for use or must be replaced.

Stability
Stability testing is ongoing and will continue during the duration of the clinical trial. Additional information about the product can be found in the Investigator's Brochure (IB).

Dose Preparation
Please refer to the Study Pharmacy Manual for CORVax plasmid preparation and handling instructions. Briefly, the Investigational Drug Product is to be prepared according to the following directions:

- Each vial contains 0.7 mL of available CORVax plasmid solution at dosing concentration of 1.67 mg/mL.
- Total dose will be 0.8 +/- 0.15 mg (see Pharmacy manual for details).
- On the day of treatment, remove the vials for each procedure from frozen storage. The research pharmacy will document time of removal (thaw start time) on an institutionally approved worksheet or the Investigational Product Formulation Worksheet.

- Remove the vials from the packaging and place at room temperature with space between the vials to allow free airflow; allow the vials to thaw completely at room temperature for approximately 5-10 minutes.
- Inspect the vials to verify contents are completely thawed.
- Thoroughly mix the vials by vigorous swirling or vortexing.
- Use standard aseptic techniques.

8.2.1 Cohorts 1A & 2A - *Intradermal* CORVax only

  - Wipe the vial and cap with isopropyl alcohol and allow to completely dry.
  - Wipe a 1000 uL pipettor with isopropyl alcohol and allow to completely dry.
  - Using a sterile tip on the 1000 uL pipettor, gently pipette up and down ten times to mix the plasmid solution.
  - Using a sterile 1 mL syringe with a 25-gauge 5/8-inch needle and needle cap, withdraw 250 uL of plasmid solution per syringe, plus additional volume as needed to prime the syringe and ensure delivery of 250 uL intradermal injection per syringe, (500 uL total).
  - Remove the needle and cap syringe(s).

- Capped syringe(s) may be placed individually in a self-sealing plastic bag and stored in a 2-8ºC temperature controlled and monitored refrigerator until ready for use.
- Discard unused portions of each vial into approved biohazard containers and dispose as per institutional requirements.
- Syringe(s) may be transported from the pharmacy to the treatment area at room temperature.
- The prepared formulation must be administered **within 8 hours** of removal from the freezer.

8.3 pIL-12 (tavokinogene telseplasmid)

How Supplied
pIL-12 is formulated in phosphate buffered saline (PBS) for direct intradermal injection followed by *in vivo* EP. GLP-grade pIL-12 is manufactured by Richter-Helm Biologics and vialed by UbiVac, and available batches will be supplied in labeled 1.25 mL screw top cryovials at a concentration of 3.3 mg/mL and fill volume of 0.3 mL.

Storage
Unopened vials of pIL-12 should be stored in the packaging received from UbiVac in a secure, continuously temperature monitored and alarmed freezer in the pharmacy or other appropriate secure location at a nominal temperature of -20ºC. Temperature variation is allowed to a maximum temperature of -10°C. Any temperature excursions greater (warmer) than -10°C must be reported to any member of the Providence Clinical team. Drug product which experiences a temperature greater (warmer) than -10°C remains suitable for clinical use provided all three of the following conditions are met:

- Maximum one temperature excursion event to temperature greater (warmer) than -10°C.
- Duration of the temperature excursion is not more than 3 hours.
- Maximum temperature achieved is not more than 5°C.

Drug product which experiences temperature excursions outside of these parameters should be immediately quarantined and reported to any member of the Providence Clinical team. Providence (clinical team) will determine whether the affected product remains suitable for use or must be replaced.

Stability
Stability testing is ongoing and will continue during the duration of the clinical trial. Additional information about the product can be found in the Investigator's Brochure (IB).

Dose Preparation Steps
Please refer to the Study Pharmacy Manual for pIL-12 preparation and handling instructions Briefly, pIL-12 is to be prepared according to the following directions:

- Each vial contains 0.3 mL of available pIL-12 solution at dosing concentration of 3.3 mg/mL.
- Total dose will be 0.8 +/- 0.15 mg (see Pharmacy manual for details).

- On the day of treatment, remove the vials for each procedure from frozen storage. The site may choose to document the time of removal (thaw start time) on the Investigational Product Formulation Worksheet or an institutionally approved worksheet.
- Remove the vials from the packaging and place at room temperature with space between the vials to allow free airflow; allow the vials to thaw completely at room temperature for approximately 5-10 minutes.
- Inspect the vials to verify contents are completely thawed.
- Thoroughly mix the vials by vigorous swirling or vortexing.
- Use standard aseptic techniques:

8.3.1 Cohorts 1B & 2B - *Intradermal* CORVax + pIL-12

  - Wipe the vial and cap with isopropyl alcohol and allow to completely dry.
  - Wipe a 1000 uL pipettor with isopropyl alcohol and allow to completely dry.
  - Using a sterile tip on the 1000 uL pipettor, gently pipette up and down ten times to mix the plasmid solution.
  - Pipette 600 uL of CORVax into 300 uL pIL-12.
  - Gently pipette up and down ten times to mix the CORVax + pIL-12 plasmid mix.
  - Using a sterile 1 mL syringe with a 25-gauge 5/8-inch needle and needle cap, withdraw 375 uL of plasmid mix per syringe, plus additional volume as needed to prime the syringe and ensure delivery 375 uL intradermal injection per syringe, (750 uL total).
  - Remove the needle and cap syringe(s).

- Capped syringe(s) may be placed in a self-sealing plastic bag and store in a 2-8ºC temperature controlled and monitored refrigerator until ready for use.
- Discard unused portions of each vial into approved biohazard containers and dispose as per institutional requirements.
- Syringe(s) may be transported from the pharmacy to the treatment area at room temperature.
- The prepared formulation must be administered **within 8 hours** of removal from the freezer.

8.4 Electroporation: IGEA CLINIPORATOR® with IGEA Applicator

CLINIPORATOR® is a medical device for electroporation.

This device shall be operated by trained medical/scientific staff who received specific training and instructed on electroporation and on the correct use of the device.

- Wear surgical gloves made of insulating material when delivering pulses and while holding the electrodes. Gloves' electrical insulation is sufficient to avoid possible electrical effects on the operator that might produce small electrical shocks or muscle contraction due to treatment's voltage and current, and possible harm to the subject as a consequence.
- Do not touch the electrode or the bushes of the handle with your fingers during the treatment.
- To avoid risks of infection for the operators, the electrode must be handled with extreme caution. Avoid contact with the pointed needles.

Electroporation is a physical phenomenon occurring in the cell membrane as cells are exposed to an electric field with proper characteristics. CLINIPORATOR® delivers voltage pulses based on standard parameters or as specified by the operator, which are then applied to the subject using the approved type of electrodes.
The potential difference due to the pulses creates an electric field which acts on the cell membrane and induces an alteration which displays at macroscopic level an increased permeability of the membrane. Molecules that normally do not go past the cell membrane either in diffusion or active transport, after electroporation can reach the intracellular environment.

Electroporation makes it possible, or rather increases the therapeutic effects of injected drugs, by temporarily increasing the cell membrane's permeability enabling the cells to absorb the injected substances.

In this study the electroporation is the basis for Electro-Gene-Transfer (EGT) to introduce DNA molecules into the cells. The device shall not be used for different purposes other than those intended.

The CLINIPORATOR® is a medical electroporation (EP) device system that consists of two main components:

1. The IGEA Electroporation System that generates electric pulses, which includes the PC Panel, the Generator and the Foot Pedal.
2. The IGEA Sterile Applicator - Model L-30-ST ("Applicator") containing an 8 needle array (2 rows of 4 needles in each row). This needle array delivers electrical pulses which enable uptake of the vaccine which was intradermally injected with a standard syringe as outlined in Section 8.3.

The Applicator contains an eight needle array with a 4.7 mm distance between the two rows of needles and 3.2 mm distance between the needles in each row. The needle length is 30 mm and the needle insertion depth can be adjusted by the user; penetration depth can be preset and locked in steps of 5mm up to a maximum of 30 mm. For this procedure, the first lock of a 5mm penetration depth will be used.

The CLINIPORATOR® is only for use with the IGEA Applicator and associated cable assembly. The IGEA Applicator will be supplied by OncoSec and should be stored in ambient conditions in a restricted area with limited access and may only be used on subjects who have been properly consented and enrolled into the investigational studies. The CLINIPORATOR® should not be used near MRI equipment and RFID systems should not be used near the CLINIPORATOR® when it is in operation. Care should be taken to ensure that the device is not used in the vicinity of flammable anesthetics. The study staff and monitors should also check the study device supplies to ensure a sufficient amount of study Applicators and cable assemblies are on hand for active subjects and that the supplies are not expired.

Storage Conditions for CLINIPORATOR®
Room temperature from -20 to 50 °C.
Relative humidity from 10% to 90%.
Atmospheric pressure from 500 to 1060 hPa.

Storage Conditions for applicator
The electrode is supplied in a sterile package. It should be kept in a dry, clean place, away from heat sources and in compliance with the following ambient conditions: Temperature: 10°C - 40°C. Sterility is guaranteed until the expiry date printed on the package, provided that the double package remains intact.

Additional details regarding handling of the device are provided in the CLINIPORATOR® User Manual.

8.4.1 All Cohorts - *Intradermal* EP

Directly following intradermal injection of the plasmid solution using a standard syringe following SOC practices for intradermal vaccine administration, the EP applicator will be applied at the appropriate depth for intradermal EP (see Section 8.5.1 for instructions), such that the electrodes span the plasmid injection site of two adjacent blebs. The applicator will be connected to the power supply and upon user activation of the attached Foot Switch, eight pulses at a field strength (E+) of 400 V/cm and pulse width of 10 ms at 300 millisecond intervals will be administered. The EP administration is anticipated to be completed in less than 1 minute. No vaccination or EP administration should be administered in the left arm.

8.5 Plasmid Injection followed by Electroporation (EP)

Participants will be treated in one of four study cohorts:

- All treatment will be delivered in the outpatient setting.
- Vaccination is delivered to right or left buttocks over the dorsogluteal muscle.
- For day 30 boost dose, any prior AEs must have resolved to grade 1 or lower as a condition of treatment.
- Each vaccination consists of two steps: intradermal injection of the plasmid solution in two divided doses of equal volume, following SOC practices for intradermal vaccine administration (akin to PPD skin test, with two adjacent blebs in this case, see Figure 3), followed by EP delivery directly over the two flattened blebs.

- Each EP complete electrical pulse delivery occurs in less than 3 seconds with total EP applicator skin contact time of less than 1 minute.

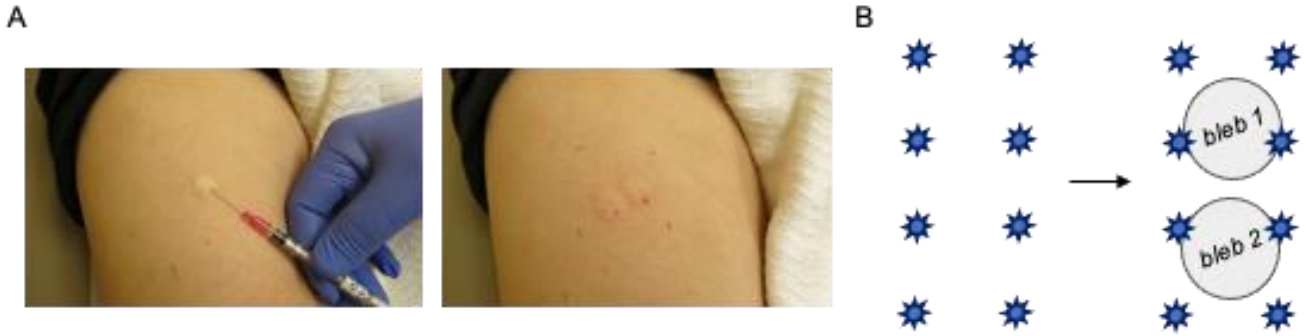


Figure 3: (A) injection technique for two adjacent intradermal blebs (photo from previous study, 0.5 mL per bleb; volumes will be lower in the current study, either 0.25 mL or 0.375 mL per bleb). (B) IGEA applicator electrode configuration relative to two intradermal injection blebs; the applicator contains an eight-needle array with a 4.7 mm distance between the two rows of needles and 3.2 mm distance between the needles in each row.

Cohorts *1A & 2A*: SARS-CoV-2 (S) protein plasmid DNA vaccine	**CORVax**

Day 1 *Intradermal*: 0.8 mg of (S) protein plasmid in 500 uL.*

*followed by CLINIPORATOR® electroporation (EP) - 8 pulses (pulse width 10 ms) of 400 V/cm.

Day 30 *Intradermal*: 0.8 mg of (S) protein plasmid in 500 uL.*

* followed by CLINIPORATOR® electroporation (EP) - 8 pulses (pulse width 10 ms) of 400 V/cm.

Cohorts *1B & 2B*: SARS-CoV-2 (S) protein plasmid DNA vaccine + pIL-12	**CORVax + pIL-12**

Day 1 *Intradermal*: 0.8 mg of (S) plasmid + 0.8 mg of pIL-12 (total volume 750 uL).*

* followed by CLINIPORATOR® electroporation (EP) - 8 pulses (pulse width 10 ms) of 400 V/cm.

Day 30 *Intradermal*: 0.8 mg of (S) protein plasmid + 0.8 mg of pIL-12 (total volume 750 uL).*

* followed by CLINIPORATOR® electroporation (EP) - 8 pulses (pulse width 10 ms) of 400 V/cm.

8.5.1 Clinical Administration Technique

Once the treatment syringe has been prepared, the syringes may be transferred to the treatment area at room temperature. The treatment syringe should be visually inspected prior to injection, checking that the solution is homogeneous. If the solution does not appear homogeneous, the plasmid should be discarded and new plasmid for treatment prepared.

Prior to plasmid injection, local anesthetics such as 1% lidocaine may be injected around the planned injection site to obtain local anesthesia. The area should be clean and wiped dry of any excess liquid prior to electroporation

procedure. Alternative local anesthetics may be used as clinically indicated and deemed clinically optimal. Icepacks to cool and numb an area are also acceptable. No systemic anesthesia should be used and the device should not be used in a room where flammable anesthetics are being used or stored. In addition, participants may be given anxiolytics (e.g., lorazepam 0.5 to 1mg PO once), and/or analgesics (e.g., ibuprofen 400 to 800mg PO once or oxycodone 5mg PO once), per institutional standard practice prior to, or during, treatment by qualified personnel (clinical RN). The options as delineated for prophylactic medication use are on par with standard practice for routine office procedures, (such as a shave biopsy) and would not be considered as adverse events. As with routine office procedures, the use of premedication is infrequent and optional; and as such, we do not see this as an impediment to widespread use of this vaccine approach during a pandemic.

General Principles:

- The intradermal injection of the plasmid solution is delivered in two divided doses of equal volume, following SOC practices for intradermal vaccine administration, (akin to PPD skin test, with two adjacent blebs in this case, see Figure 3). Injection is performed prior to electroporation.
- Electroporation (EP) must be co-localized at the site of the two adjacent flattened blebs from intradermal syringe injection, and should be done as soon as reasonably possible following injection.
- The EP applicator should be preset and locked at the 5mm penetration depth. This depth is maintained by pressing the applicator flush to subject's skin during the electroporation procedure.
- The anticipated total time of EP applicator contact with the subject's skin is less than 1 minute.
- Detailed instructions are provided in the CLINIPORATOR® User Manual, which should be reviewed prior to the start of treatment.

8.5.2 Monitoring Plan on Day of Administration

Participant vital signs will be measured twice every 30 minutes, starting within 10-15 minutes post vaccination. The study investigator will review vitals prior to release from clinic.

8.5.3 Cohorts 1A & 2A: CORVax

1. *Intradermal*: injection of CORVax 0.8 mg in 500 uL, followed directly by EP (e.g. right or left buttocks over the dorsogluteal muscle); record pain score 5 minutes post.

8.5.4 Cohorts 1B & 2B: CORVax + pIL-12

1. *Intradermal:* injection of CORVax + pIL-12 in 750 uL (0.8 mg in 500 uL of CORVax + 0.8 mg in 250 uL of pIL-12), followed directly by EP (e.g. right or left buttocks over the dorsogluteal muscle); record pain score 5 minutes post.

8.6 Durable Procedural Pain Assessment

Based on clinical data, it is expected that subjects will experience a transient pain associated with the procedure of EP that dissipates shortly thereafter[28]. EP-associated pain assessment monitoring will be performed days 1 and 30 at the start of each treatment and 5 minutes after EP procedure. Only pain that persists >5 minutes after the end of EP procedure will be evaluated on numeric pain rating scale and documented as an AE per the CTCAE (active version). Numeric pain rating scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli, on a scale of 0 to 10 with a score of zero denoting "no pain at all" and a score of 10 denoting "worst possible pain" [29–32].

8.7 Management of Clinical Toxicity

Subjects will be monitored during and after vaccine injection and electroporation. Vital signs will be measured as specified in Section 8.5.2. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) may be administered for

treatment-related reactions at the discretion of the investigator. As with any vaccine therapy, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. There will be no dose modifications in this study.

8.8 Reporting Product Complaints

Any defects with the investigational product must be reported immediately to the OncoSec Medical Incorporated Clinical Development Department by the site with further notification to the site monitor. All defects will be communicated to OncoSec and investigated further with the Quality Assurance and Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed. OncoSec contact information for reporting product complaints:

Email: kmalloy@oncosec.com
Tel: +858.375.9989

Mail: OncoSec Medical Incorporated
Attn: Clinical Development – Re: Product Complaint
24 N Main Street, Pennington NJ 08540

9. IMMUNODYNAMIC BIOMARKERS

9.1 Immunologic Monitoring

Blood sampling for plasmid expression levels and immune response measurements will occur on days 1, 2, 3, 15, 30, 31, 32, 45, 60 and 90 of study. The main objectives of the monitoring will be to characterize both the antibody and cellular immune response to the pUMVC3-CORVax vaccine. The sites performing these studies will include the Earle A. Chiles Research Institute Laboratories, (Immune Monitoring Laboratory (IML), Molecular and Tumor Immunology Laboratory (MTI), Laboratory of Cancer Immunobiology (LCI) and Molecular Pathology Laboratories (MPL)) or outside vendors selected by the Principle Investigator and research team. Blood will be processed and cryopreserved for subsequent monitoring or flow cytometry with a panel of markers will be run the day blood is drawn. At a minimum the panels will include CD4, CD8, NK, and B cells. If NIAID or other grant resources become available additional monitoring is planned and may include CD4 T conventional, Treg, T memory, Ki-67, CD38, HLA-DR, CD40, ICOS, granzyme B, PD-1, TIM-3, LAG-3, 4-1BB, CTLA-4, OX40R, NKG2A, CD94, NKp46, NKG2D, NKp30, CD158e1, KIRc, CD158b, CD11b, CD15, CD33, CD54, CD80, CD83, CD86, PD-L1, PD-L2. Sorted immune cell subsets could also be submitted for RNA/DNA extraction and genome-wide CpG methylation by target-capture DNA library preparation and Illumina sequencing.

9.2 Neutralization assay

Antibody neutralization of the SARS-CoV-2 will be assessed using a pseudotyped lentivirus expressing the SARS-CoV-2 (S) protein and luciferase. Readout will be the ability of sera from vaccinated candidates to prevent infection of susceptible target cells. Alternatively, a surrogate viral neutralization test, reporting ability of sera to block hACE2R binding to spike will be performed.

9.3 Cytokines

If grant support is available, serum cytokine profiling will be performed using the Quanterix Simoa platform evaluating systemic IL-12p70 as well as 35 additional cytokines including IFN-gamma, TNF-alpha, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-17A and TGF-beta.

9.4 T cell response

SARS-CoV-2 (S) protein-specific cellular immune responses will be measured by cytokine-release assay for type I, type 2 and IL-17 cytokine responses using cytokine bead arrays. IFN-gamma positive responses will be assessed by interferon-gamma ELISA and either intracellular cytokine staining (ICS) or ELISPOT assay using unfractionated PBMC and peptide pools of epitopes considered to be dominant epitopes for the HLA expressed by the specific subject. If predicted HLA-binding epitopes fail to identify targets of immune response, peptide pools containing 15-mer peptides overlapping by 11 amino acids will be explored. Our prediction is that the cytokine response to whole protein will be dominated by CD4+ T-cell response and that the response to overlapping peptides will comprise both CD4+ and CD8+ T-cell responses.

9.5 B cell response

Analysis of antibody responses to SARS-CoV-2 spike (S) glycoprotein will be performed using Microaffinity proteomic (MAP) bead technology or ELISA. Bead arrays containing SARS-CoV-2 proteins will be used to assess IgM and the isotype of IgG responses that develop following vaccination. Humoral response will also be monitored by B-Cell ELISPOT evaluating PBMC for IgA, IgM, and IgG response to the COVID-19 S spike to determine the B cell response that has developed.

9.6 Coordinated humoral/cellular response

Grant support is being requested to perform single-cell RNA sequencing at day 0, 15, 30, 45, 60 and 90. It is planned that paired αβ TCRseq and tandem BCRseq using the Archer Immunoverse platform will allow tracking of T and B cell clones and provide opportunities to assess whether dominant clones recognize epitopes of the SARS-CoV-2 spike protein. We have successfully used this technology to isolate tumor-reactive TCRs from peripheral blood of subjects on a cancer vaccine trial[33]. We postulate that persisting neutralizing Ab responses will result from a coordinated CD4, CD8 and B cell response to the SARS-CoV-2 spike (S) glycoprotein.

9.7 Whole genome sequencing

Whole genome sequencing will be performed to assess polymorphisms in immune-response related genes. It will also provide the HLA haplotypes. This information will be evaluated for relationships to the magnitude of the immune response to vaccination. The studies performed here, while only a small number of subjects and some of which are exploratory in nature, may provide insights into the apparently unique biology of this virus. We will also look for correlations with the depth and magnitude of response to vaccination.

9.8 Clinical Outcomes and Surveillance Database

A coded, de-identified clinical database will be maintained by the study PI or clinical research as delegated by the study PI. The database and codes key will be housed on a password and encryption protected network drive, only accessible to the study PI and delegated staff. Participants will provide consent for inclusion in the longitudinal study database at enrollment. Clinical data will be collected from time of enrollment to a minimum of five years clinical surveillance post completion of treatment, or death or loss to follow-up. Such data will include but not be limited to: age at time of study, medications, medical and surgical history.

10. REGULATORY & REPORTING REQUIREMENTS

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) active version. The CTCAE active version can be accessed from the CTEP home page (http://ctep.cancer.gov).

10.2 Definitions

Serious adverse event:
A serious adverse drug or device experience is defined as any adverse drug or device experience occurring at any

dose or experience with the device that results in any of the following outcomes: Death, a life-threatening adverse drug or device experience, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug or device experience when, based upon appropriate medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected adverse event:
Any adverse drug or device experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Associated with the use of the drug / device / intervention:
There is a reasonable possibility that the experience may have been caused by the drug or device.

Disability:
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse event:
Any adverse drug or device experience that places the participant or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Unanticipated Problem
An unanticipated problem is an adverse event that is (i) unexpected; (ii) serious; and (iii) felt by the investigator to be possibly, probably, or definitely related to the research intervention. Only adverse events that meet this definition need be reported to the IRB.

For more information on the definition of an unanticipated problem and reporting requirement, consult the current PH&S AE Guidelines published on the IRB website (http://phsnet.phsor.org/institutional_review_board).

10.3 Adverse Event Reporting

PSJH IRB
An unanticipated event that is serious and definitely or probably caused by the study treatment (drugs or device) will be reported to the IRB in accordance with their guidelines and within their timelines.

FDA Reporting
The Principal Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32). A suspected adverse reaction must be both serious and unexpected in order to meet the reporting requirements.

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure, the device user manual, or is not listed at the specificity or severity that has been observed; or, if an investigator brochure or device user manual is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator, it results in any of the following outcomes: Death, a life-threatening adverse event, hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The timeline for submitting an IND safety report to FDA is no later than 15 calendar days after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than 7 calendar days after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Any potentially vaccine-related immune-mediated medical condition (see Appendix 2) that occurs will be considered unexpected. Expedited reporting requirements (as outlined in 21 CFR 312.32) will be followed for any adverse event assessed as a serious and unexpected suspected adverse reaction (SUSAR).

10.4 Continuing Review and Final Reports

An annual progress report (continuing review) will be submitted to the IRB for the duration of the study. A final report to the IRB will be submitted at the summation of the study.

All IND annual reports, clinical trial reports, and clinical trial report addenda submitted to the FDA will include tabulated summaries of available adverse event data for potentially immune-mediated medical conditions reported during the trial, categorized by MedDRA term. These summaries will include any conditions reported during the trial that match the terms listed in Appendix 2, as well as any other potentially immune-mediated medical conditions (pIMMCs) reported during the trial that do not appear on the list in Appendix 2. For each adverse event included in the summaries, a case narrative will be provided, along with an assessment of the seriousness of the event and causal relationship to study vaccine, as required by 21 CFR 312.32.

Collection of MAAE data beyond 6 months after the last study vaccination will not delay submission of clinical trial reports and initiation of subsequent clinical trials, and final analyses of MAAEs may be submitted in clinical trial report addenda.

The safety analysis in the final clinical study report will include the number and proportion of subjects in each cohort reporting 1) each solicited AE of any grade through seven days following any dose and each dose, 2) each solicited AE grade 3 and greater within seven days following any dose and each dose, 3) unsolicited AEs of any grade reported at a minimum through 28 days following dose 2, 4) unsolicited AEs grade 3 and greater reported at a minimum through 28 days following dose 2, 5) SAEs within 28 days following dose 2, 6) SAEs, MAAEs, and pIMMCs reported through one year following dose 2. In addition, it will include the number and proportion of subjects in each cohort of each category of AE that the investigator assessed as related.

10.5 Protocol Modifications and Amendments

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be approved by IRB prior to implementation. If it becomes necessary to alter the protocol to eliminate an immediate hazard to Participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

10.6 Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends. The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed participant consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the

application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10.7 Oversight and Monitoring Plan

Oversight of participant safety will include review of adverse events as well as study progress and outcomes. Adverse events, outcomes, and recruitment and retention of Participants will be reviewed on a weekly basis by the PI, research nurse, and data coordinator. Protocol deviations are reviewed monthly at the Providence Cancer Institute's Quality Assurance Committee meetings (monthly). Study monitoring activities (Quality Control Reviews) are performed by clinical research staff members who have completed specialized training in study monitoring procedures and human subjects' protections. Individuals who perform study monitoring activities do not report to Principal Investigators or research scientists and may not monitor studies for which they have direct responsibility. Results of study monitoring activities will be reported to applicable study personnel, Clinical Research Program Managers and Quality Assurance. Study monitoring activities are conducted regularly and include (but are not limited to) review and verification of the following:

- Eligibility
- Informed Consent process
- Adherence to protocol treatment plan
- Case Report Forms (CRFs)
- Source Documentation
- Adverse Events
- Regulatory Reporting

10.8 Quality Assurance

Quality Assurance (QA) personnel review study monitoring reports and if necessary, determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant participant safety issues are identified. QA will track and trend results from study monitoring reports as well as associated corrective and preventive actions. A QA summary report will be provided to the IRB at the time of continuing review. QA personnel do not have a direct reporting relationship to the Principal Investigator and are not responsible for enrollment or coordination of care for study participants.

10.9 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into Velos eResearch via eCRFs. The Clinical Research Associate (CRA) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs. The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's electronic medical records. All printed source documentation should be kept in separate research folders for each participant.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size and Statistical Analysis

Sample size: 36 participants will be enrolled and assessed for safety in one of four study cohorts (9 participants per cohort). Participants who enroll but do not complete therapy for reasons other than DLT may be replaced.

Statistical analysis: The safety evaluation will be based on the treated population, which includes all participants who receive any investigational product. Demographic and baseline characteristics will be summarized with means, medians, standard deviations, ranges or percentages. Safety will be summarized by the percentage of participants with adverse events, with grading according to the Common Terminology Criteria for Adverse Events (CTCAE, active version).

11.2 Participant Accrual

We do not foresee barriers to accrual of healthy adult volunteers, in light of the recent Seattle experience with rapid accrual of healthy volunteers to a comparable SARS-CoV-2 phase I vaccine study. Individuals will not be reimbursed for participation in this study.

APPENDIX 1: Toxicity Grading Scale

Adapted from "FDA Guidance for Industry 2005D-0155: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" accessible at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical

Tables 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, > 72 hours	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest > 72 hours	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm > 72 hours	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity > 72 hours	Necrosis

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

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4; 100.4 – 101.1	38.5 – 38.9; 101.2 – 102.0	39.0 – 40; 102.1 – 104 symptomatic for >24	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130 for > 24 hours and symptomatic	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45 for > 24 hours and symptomatic	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155 for > 48 hours and symptomatic	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100 for > 48 hours and symptomatic	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80 and symptomatic	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25 and symptomatic	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** 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 and requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools/24 hours and 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 lasting > 48 hours	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity lasting > 72 hours	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

Tables for Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--

Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1–10 xULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters at the time of the study. Institutional normal reference ranges should be provided to the investigator for final grade assignment.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

*** "ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.3 x ULN	> 1.3 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to the investigator for final grade assignment.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX 2: Medically Attended Adverse Events - pIMMCs

List of Potentially Immune-Mediated Medical Conditions (pIMMCs)

Gastrointestinal disorders
Celiac disease
Crohn's disease
Ulcerative colitis
Ulcerative proctitis

Liver disorders
Autoimmune cholangitis
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis

Metabolic diseases
Addison's disease
Autoimmune thyroiditis (including Hashimoto thyroiditis)
Diabetes mellitus type I
Grave's or Basedow's disease

Musculoskeletal disorders
Antisynthetase syndrome
Dermatomyositis
Juvenile chronic arthritis (including Still's disease)
Mixed connective tissue disorder
Polymyalgia rheumatic
Polymyositis
Psoriatic arthropathy
Relapsing polychondritis
Rheumatoid arthritis
Scleroderma, including diffuse systemic form and CREST syndrome
Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
Systemic lupus erythematosus
Systemic sclerosis

Neuroinflammatory disorders
Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
Multiple sclerosis
Narcolepsy
Optic neuritis
Transverse myelitis
Myasthenia gravis, including Eaton-Lambert syndrome

Skin disorders
Alopecia areata
Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
Cutaneous lupus erythematosus

Erythema nodosum
Morphoea
Lichen planus
Psoriasis
Rosacea
Sweet’s syndrome
Vitiligo

Vasculitides
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger’s disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others
Antiphospholipid syndrome
Autoimmune hemolytic anemia
Autoimmune glomerulonephritis (including IgA nephropathy,
glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
Autoimmune myocarditis/cardiomyopathy
Autoimmune thrombocytopenia
Goodpasture syndrome
Idiopathic pulmonary fibrosis
Pernicious anemia
Raynaud’s phenomenon
Sarcoidosis
Sjögren’s syndrome
Stevens-Johnson syndrome
Uveitis

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