STUDY PROTOCOL

A Phase I, Prospective, Open-Labeled Study to Evaluate the Safety and Immunogenicity of MVC-COV1901

Protocol Number: **CT-COV-11**

Investigational product: **MVC-COV1901**

Sponsor: **Medigen Vaccine Biologics Corp.**

Version Number: **V2.0, 31DEC2020**

Confidentiality Statement

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PROTOCOL APPROVAL PAGE

Protocol Number: CT-COV-11

Version: 2.0

Date: 31DEC2020

Sponsor Approval(s):

[redacted]

Medical Affairs Associate Director,

Medigen Vaccine Biologics Corp.

Signature Date

STATEMENT OF COMPLIANCE

The signature below constitutes the approval of this protocol and the attachments and assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines. No deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Principal Investigator:

Affiliation:

Address:

Phone:

Signature: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase I, Prospective, Open-Labeled Study to Evaluate the Safety and Immunogenicity of MVC-COV1901

Protocol Number: CT-COV-11

Sponsor: Medigen Vaccine Biologics Corp.

Study Description: This is a phase I prospective, open-labeled, single-center study to evaluate the safety and immunogenicity of MVC-COV1901.

This study is a dose escalation study with three separate sub-phases for subjects ≥20 and <50 years of age. Each sub-phase will consist of 15 subjects. Each subject is to complete at least one vaccination.

Phase 1a: 4 sentinel subjects will be recruited to receive 5 mcg S-protein with adjuvant MVC-COV1901 to evaluate preliminary safety data of the vaccine. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1a, dosing of the remaining subjects in Phase 1a and Phase 1b will proceed.

Phase 1b: Another 4 sentinel subjects will be enrolled to receive 15 mcg S-protein with adjuvant MVC-COV1901 in Phase 1b. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1b, dosing of the remaining subjects in Phase 1b and Phase 1c will proceed.

Phase 1c: Another 4 sentinel subjects will be enrolled to receive 25 mcg S-protein with adjuvant MVC-COV1901. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1c, dosing of the remaining subjects in Phase 1c will proceed.

If any ≥ Grade 3 AE or SAE occurs, DSMB will evaluate preliminary safety data and determine if it remains acceptable to continue dosing.

The vaccination schedule consists of two doses of MVC-COV1901 for each study subject, administered by intramuscular (IM) injection 0.5mL in the deltoid region of non-dominant arm preferably 28 days apart, on Day 1 and Day 29.

An interim analysis of immunogenicity data for at least the sentinel subjects in each sub-phase (total 12 subjects) and safety data from baseline to 28 days after second vaccination for all subjects will be carried out when all the subjects complete V8 (28 days after the second vaccination).

Objectives: **Primary Objective:**

To evaluate the safety of MVC-COV1901 in three different strengths (5, 15, and 25 mcg S-protein with [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant) from V2 (Day 1) to V8 (28 days after second vaccination).

Secondary Objective:

1. To evaluate the immunogenicity in terms of neutralizing antibody titers and binding antibody titers 14 days, 28 days after each vaccination, 90 days and 180 days after second vaccination.
2. To evaluate the immunogenicity in terms of cellular immune responses 28 days after second vaccination and 180 days after second vaccination.
3. To evaluate the safety of MVC-COV1901 within the whole study period.

Endpoints:

Primary Endpoints:

The safety of MVC-COV1901 in terms of laboratory assessments, the occurrence rate of solicited adverse events (including administration site events: pain, erythema/redness, induration/swelling; and systemic events: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea), unsolicited adverse events, other AEs, adverse event of special interest (AESI) and serious adverse events (SAEs) from V2 (Day 1) to V8 (28 days after second vaccination).

Secondary Endpoints:

1. Neutralization titers in terms of Geometric mean titer (GMT), Seroconversion rate (SCR), and GMT ratio at Visit 4, 5, 7, 8, 9 and 10. SCR is defined as the percentage of subjects with ≥ 4-fold increase in titers from the baseline. GMT ratio is defined as geometric mean of fold increase of post-vaccination titers over the baseline titers.
2. Antigen specific immunoglobulins in terms of GMT, SCR and GMT ratio at Visit 4, 5, 7, 8, 9 and 10.
3. Antigen specific cellular immune responses as determined by interferon-gamma (IFN-γ) ELISpot、interleukin (IL)-4 ELISpot at Visit 8 and 10.
4. Antigen specific cellular immune responses as determined by multi-parameter intracellular cytokine staining (including CD3, CD4, CD8, IFN-γ, IL-2 and IL-4, etc.) flow cytometry at Visit 8 and 10.
5. Safety of MVC-COV1901 in terms of other adverse events, AESI and SAEs within the study period.

Study Population: A total of 45 subjects are planned to be enrolled in staggered manner.

Group	N	Formulation
1a	15	5 mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant
1b	15	15 mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant
1c	15	25 mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant

Phase: I

Study Intervention: Investigational Product MVC-COV1901

5 mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant

15 mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant

25mcg S-protein + [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant

Inclusion Criteria

1. Male or female healthy volunteer ≥20 and <50 years of age
2. Subject free of ongoing acute diseases or serious medical conditions (e.g. concomitant illness) such as cardiovascular (e.g. New York Heart Association grade III or IV), hepatic (e.g. Child-Pugh Class C), psychiatric condition (e.g. alcoholism, drug abuse), medical history, physical findings, or laboratory abnormality that in the investigator's opinion could interfere with the results of the trial or adversely affect the safety of the subject
3. Female subject must be:
   - Either of non-childbearing potential, i.e. surgically sterilized (defined as having undergone hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy; tubal ligation alone is not considered sufficient) or one year post-menopausal;
   - Or, if of childbearing potential, must be abstinent or agree to use medically effective contraception from 14 days before screening to 30 days following last injection of study vaccines. Acceptable forms include:
     - ✓ Implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)
     - ✓ Established use of hormonal methods (injectable, pill, patch or ring) combined with barrier methods of contraception:

condom, or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Have a negative pregnancy test

4. Subject is willing and able to comply with all required study visits and follow-up required by this protocol
5. Subject has no overseas travel within 14 days of screening and will not have any throughout the study period
6. Subject must provide written informed consent or the Subject's legal representative must understand and consent to the procedure

Exclusion Criteria

1. Receiving any investigational intervention either currently or within 30 days of first dose;
2. Subject (particularly who is a healthcare worker) with previous known or potential exposure to SARS CoV-1 or 2 viruses (**EXCEPT** for those who have been tested negative and the 14-days self-managements/ home quarantines/ home isolations are completed), or received any other COVID-19 vaccine;
3. Administration of any vaccine within 4 weeks of first dose;
4. A BMI greater than or equal to 30 kg/m^2;
5. Subject with a history of hypersensitivity to any vaccine or a history of allergic disease or reactions likely to be exacerbated by any component of the MVC-COV1901;
6. Administration of any blood product or intravenous immunoglobulin administration within 12 weeks of first dose;
7. Pregnancy or breast feeding or have plans to become pregnant in 30 days after last injection of study vaccines;
8. History of positive serologic test for HIV, hepatitis B surface antigen (HBsAg) or any potentially communicable infectious disease as determined by the investigator or Medical Monitor;
9. Positive serologic test for hepatitis C (**EXCEPTION**: successful treatment with confirmation of sustained virologic response);
10. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 mg/dL;
11. Screening laboratory tests with Grade 2 or higher abnormality (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007);
12. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;
13. A history of autoimmune disease (systemic lupus, rheumatoid arthritis, scleroderma, polyarthritis, thyroiditis, etc.);
14. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or less than prednisone 20 mg/day or equivalent) within 12 weeks of first dose;

15. Current or anticipated treatment with TNF-α inhibitors, e.g. infliximab, adalimumab, etanercept within 12 weeks of first dose;
16. Prior major surgery or any radiation therapy12 weeks of first dose;
17. Alcohol or drug abuse or dependence, psychiatric, addictive, or any disorder that, in the opinion of the investigator, would interfere with adherence to study requirements or assessment of immunologic endpoints; or any illness or condition that in the opinion of the investigator may affect the safety of the participant or the evaluation of any study endpoint;
18. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition, tattoos or wound covering the injection site area;
19. Body (oral, rectal or ear) temperature ≥ 38.0°C or acute illness within 2 days of first dose, or acute respiratory illness within 14 days of first dose;
20. Screening laboratory test of antinuclear antibody (ANA), anti-dsDNA antibody, anti-neutrophil cytoplasmic antibodies (ANCA, including cytoplasmic ANCA (c-ANCA), perinuclear ANCA (p-ANCA)) with the value higher than upper normal limit;
21. Abnormal screening electrocardiography (ECG) with clinically significant findings as reviewed by investigator.

Statistical Analysis

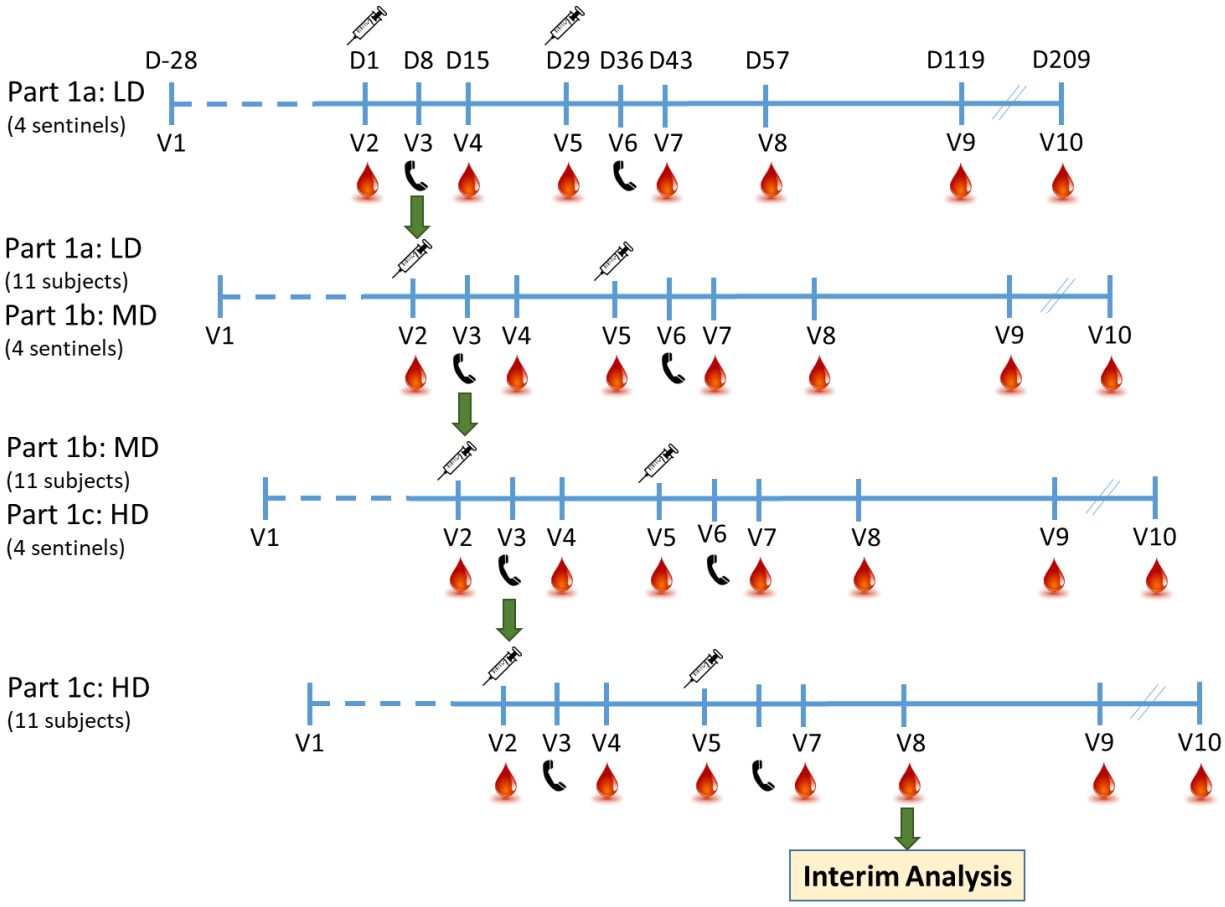
All results will be presented using descriptive statistics. Significance tests (2-tailed, alpha=0.05) without alpha adjustment will be performed for pairwise comparison where appropriate and p-values will be rounded to four decimal places if applied.

Regarding descriptive statistics, continuous variables will be summarized with number of subject, mean, standard deviation, median, range as well as 95% confidence interval, IQR, and 95% confidence interval based on median; while number and percentage of subject for categorical variables.

Study Duration: Estimated 12 months

Participant Duration: Estimated 8 months

1.2 SCHEMA


D-28
D1
D8
D15
D29
D36
D43
D57
D119
D209
Part 1a: LD
(4 sentinels)
V1
V2
V3
V4
V5
V6
V7
V8
V9
V10
Part 1a: LD
(11 subjects)
Part 1b: MD
(4 sentinels)
Part 1b: MD
(11 subjects)
Part 1c: HD
(4 sentinels)
Part 1c: HD
(11 subjects)
Interim Analysis

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Unscheduled[14]
Visit Day	-28 ~ -1	1	8 (±2)	15 (±3)	29 (±3)	36 (7±2 days after V5)	43 (14±3 days after V5)	57 (28±3 days after V5)	119 (90±7 days after V5)	209 (180±14 days after V5)	NA
Procedures \ **Type**	Screening	Vaccination 1	Phone Call	Safety and Immunogenicity Visit	Vaccination 2	Phone Call	Safety and immunogenicity Visit	Immunogenicity Visit	Immuno-genicity Visit	EOS	NA
Informed consent	X										
Medical history	X	X									
Demographics	X										
Concomitant medication[1]	X	X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion criteria	X	X									
Urine pregnancy test[2]	X	X			X						Per investigator's decision
Body height and weight	X										
ECG	X	X[15]		X	X[15]		X			X	
Physical examination[3]	X[3a]	X[3a]		X[3a]	X[3a]		X[3a]	X[3b]	X[3b]	X[3b]	
Serology test[4]	X										
Hematology, biochemistry, and immunology tests[5]	X			X	X		X	X			
Vital signs[6]	X	X			X						
Elimination criteria[7]			X	X	X	X	X	X	X	X	
Contraindication to vaccine[8]		X			X						
Immunogenicity test[9]		X		X[9a]	X[9a]		X[9a]	X	X[9a]	X	
Vaccination[10]		X			X						
Distribution of diary		X			X						

cards											
Diary cards review and return				X			X				
Solicited symptoms[11]		X[13]	X		X	X					Per investigator's decision
Unsolicited symptoms[12]		X[13]	X	X	X	X	X	X			
Other AEs		X[13]	X	X	X	X	X	X	X	X	
AESI/SAEs		X[13]	X	X	X	X	X	X	X	X	
Study completion										X	

1. Concomitant medication recorded prior to 1st vaccination is considered as medication history.
2. Urine pregnancy test (Beta-hCG): for female subjects with child bearing potential only
3. Full physical examination (3a) performed at Visit 1, 2, 4, 5, and 7; (3b) perform targeted examinations at Visit 8, Visit 9 and 10 as determined by Investigator or per participant complaints;
4. Serology includes: HIV-1 and HIV-2 antibody or rapid test, HBsAg, HCV antibody
5. Hematology: includes hemoglobin, red blood cell, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell, differential of leukocytes, platelets, prothrombin time (PT) and activated partial thromboplastin time (APTT). Biochemistry: includes Sodium (Na), potassium (K), chloride (Cl), fasting glucose, blood urea nitrogen (BUN), Creatinine, alanine transferase (ALT), aspartate aminotransferase (AST), Creatine phosphokinase. Immunology: ANA, anti-dsDNA antibody, ANCA (c-ANCA and p-ANCA).
6. Vital Signs: Body temperature, pulse rate, respiratory rate and blood pressure at sitting position. Vital signs will be performed pre vaccination and 1 hour after vaccination at V2 and V5.
7. Elimination criteria: administration of prohibited medication/treatment, confirmed COVID-19 infection by available medical records or confirmed definition of Taiwan CDC, any pathological event, clinical adverse event, or any change in the subject's status giving indication to the investigator that further vaccination of investigational product may not be the best interest of the subject, pregnancy, any vaccine-related SAE during the study period
8. Contraindication to vaccine: body (oral, rectal or ear) temperature≥38.0°C or acute illness within 2 days before vaccination, any inactivated vaccine use within 7 days of vaccination visit, any live-attenuated vaccine use within 28 days of vaccination visit, or any condition that is a contraindication to vaccination based on the judgement of investigator.
9. Immunogenicity test: humoral and cell-mediated immune responses; (9a) humoral immune responses only
10. Vaccination: Before vaccination, physical examination, medical history (V2 only), pregnancy test for applicable subjects, immunogenicity test, vital signs, contraindication to vaccine and elimination criteria will be done or assessed. Subject will be observed for at least 1 hour (2 hours for the first four subjects at V2) for vital signs, or any immediate adverse reactions.
11. Solicited AEs are defined as administration site events (pain, erythema/redness and induration/swelling) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea) in 7 days after each vaccination. Unscheduled visit will be arranged when investigator or medical monitor considers necessary.

12. Unsolicited AEs are any untoward medical events other than solicited AEs occurred in 28 days after each vaccination.
13. All AEs will be recorded after vaccination.
14. Unscheduled visit will be arranged when investigator or medical monitor considers necessary.
15. ECG will be performed pre vaccination and 1 hour after vaccination at V2 and V5.

2 INTRODUCTION

2.1 STUDY RATIONALE

Coronaviruses are large enveloped positive-sense RNA viruses that are characterized by club-like spikes that project from their surfaces and a unique replication strategy, with the ability to cause a variety of diseases in mammals, birds, and humans (Fehr and Perlman, 2015). The coronaviruses are zoonotic in nature, and can manifest on humans symptoms ranging from mild cold to more severe respiratory, enteric, hepatic and neurological symptoms (Zhou et al 2020). In December 2019, clusters of patients were reported with pneumonia of unknown cause in Wuhan, Hubei Province, China. Phylogenetic studies revealed that the virus was genetically related to two bat coronaviruses, and was sufficiently different from SARS-CoV and MERS-CoV to be considered a new human-infecting betacoronavirus (Lu et al, 2020; Zhu et al 2020). The virus was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (ICTV), and the disease caused by the virus was also subsequently named coronavirus disease-2019 (COVID-19) (Gorbalenya et al 2020, WHO Situation Report 22).

Human infections due to SARS-CoV-2 began to spread globally following the outbreak in Wuhan, China. On January 30th 2020, a WHO panel declared the COVID-19 outbreak as a public health emergency of international concerns (WHO), and this outbreak was also subsequently characterized as a pandemic declared by the WHO on March 11th, 2020 (WHO media briefing, March 11th). COVID-19 was found to have a more severe transmissibility and pandemic risk than the previous SARS-CoV outbreak in 2003, and the average incubation duration of COVID-19 was estimated to be 4.8±2.6, ranging from 2-11 days (Liu et al 2020). True case fatality rate remains unknown at the time of outbreak, but it has been estimated that the case fatality risk estimates for COVID-19 lies within a broad range of 0.25%-3% (CDC, EID Journal). On December 1st, 2020, WHO released a COVID-19 Weekly Epidemiological Update stating that as of 29 November, there have been over 61.8 million cases and over 1.4 million deaths reported globally since the start of the pandemic, with numerous countries being affected by the pandemic (WHO Weekly Epidemiology Update on COVID-19, 1 December 2020).

Globally, humans infected with SARS-CoV-2 have clinical presentation with a wide range of severity, ranging from asymptomatic to severe and even fatal illness. Common symptoms at onset of illness include fever (83%-98%), cough (76%-82%), dry cough (59%) and myalgia or fatigue (44-70%), and less common symptoms included sputum production (28%), headache (8%), hemoptysis (5%) and diarrhea (2%-3%). Lab abnormalities included lymphopenia (70%), prolonged PT (58%), and elevated LDH (40%). 31%-55% of patients developed dyspnea (median time 5.0-8.0 days), and all patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (16%-29%), acute cardiac injury (12%) and secondary infections (10%). ICU admission rate was estimated to be 26%-32%, and the overall mortality rate was 4.3%-15% (Huang et al 2020, Wang et al 2020, Chen et al 2020). The mortality rate of COVID-19 worldwide is approximately 2.4%, which are the results of multi-organ failure especially in the elderly population and those with underlying health conditions (Prompetchara et al 2020).

Currently, there is no specific treatment for COVID-19 and there is no vaccine available to prevent the disease. Clinical management for diagnosed patients include symptomatic treatment

and supportive care, together with infection prevention and control measures to prevent further spread of COVID-19 (CDC interim guideline). Due to the highly contagious nature of SARS-CoV-2, possibly due to transmission via asymptomatic infected individuals, a vaccine against COVID-19 would have a major impact and contribution to global public health.

2.2 BACKGROUND

Subunit vaccines are vaccines that contain only the antigenic parts of the pathogen, which are necessary to elicit a protective immune response. A number of subunit vaccines against SARS-CoV and MERS-CoV are being developed, and the targets used include the full-length S (spike) protein, the RBD (receptor binding domain), non-RBD S protein fragments, and non-S structural proteins (Wang et al 2020). Studies have shown that the genomic sequence of SARS-CoV-2 is almost identical to and share 79.6% sequence identity to the SARS-CoV virus, and it has also been elucidated that the SARS-CoV-2 genome encodes the open reading frame (ORF), four structural proteins consisting of S (spike), E (envelope), M (membrane), and N (nucleocapsid); as well as six accessory proteins (Zhou et al 2020).

The S protein of the SARS-CoV-2 is a trimeric class I fusion protein that exists in a metastable pre-fusion conformation, and structural changes of the protein allow fusion of the viral membrane with host-cell membrane. The SARS-CoV-2 virus makes use of the densely glycosylated spike protein to gain entry into host cells, resulting in viral infection (Wrapp et al 2020, Walls et al 2020). It has also been discovered that SARS-CoV-2 utilizes ACE2 receptor to enter target cells (Zhou et al 2020, Wrapp et al 2020).

MVC-COV1901 is an adjuvanted subunit vaccine comprising a modified form of spike protein of SARS-CoV-2 (5 mcg, 15 mcg or 25 mcg), known as S-2P protein and supplied in a pre-filled syringe in 0.5 mL buffer solution. This trial will test for safety and immunogenicity of the MVC-COV1901.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 POTENTIAL RISKS

Vaccines in general are associated with common local reactions including pain, swelling, and erythema at the injection site, and systemic reactions including fever, irritation, drowsiness and potentially rash. Though rare, serious adverse reactions are sometimes associated with certain types of vaccine. For example, it has been described that rotavirus vaccine may be associated with intussusception (1 per 20,000 to 100,000 doses), and that MMR vaccine may be associated with immune thrombocytopenic purpura (1 per 20,000 doses) (Spenser et al 2017). Vaccine with CpG as adjuvant are associated with adverse reactions including injection site pain (23%-39%), fatigue (11%-17%), and headache (8%-17%) (Heplisav-B, 2020).

2.3.2 POTENTIAL BENEFITS

Protection against the SAR-CoV-2 which has demonstrated high transmissibility not only benefits individuals, but would also have a great impact on public health.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The COVID-19 pandemic has resulted in more than 500,000 deaths worldwide, and governments across many countries have implemented measures such as social distancing, lockdowns and quarantine orders to prevent further spread of the virus. The public health emergency have resulted in economy crisis. Vaccines can prevent the spread of COVID-19, protecting individuals and communities against the SARS-CoV-2 infection. It is therefore believed, the potential benefit of MVC-COV1901 outweighs its potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the safety of MVC-COV1901 in three different strengths (5, 15, and 25 mcg S-protein with [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant) from V2 (Day 1) to V8 (28 days after second vaccination).	The safety of MVC-COV1901 in terms of laboratory assessments, the occurrence rate of solicited adverse events (including administration site events: pain, erythema/redness, induration/swelling; and systemic events: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea), unsolicited adverse events, other AEs, adverse event of special interest (AESI) and serious adverse events (SAEs) from V2 (Day 1) to V8 (28 days after second vaccination).
Secondary	
1. To evaluate the immunogenicity in terms of neutralizing antibody titers and binding antibody titers 14 days, 28 days after each vaccination, and 90 days and 180 days after second vaccination. 2. To evaluate the immunogenicity in terms of cellular immune responses 28 days after second vaccination and 180 days after second vaccination. 3. To evaluate the safety of MVC-COV1901 within the whole study period.	1. Neutralization titers in terms of Geometric mean titer (GMT), Seroconversion rate (SCR), and GMT ratio at Visit 4, 5, 7, 8, 9 and 10. SCR is defined as the percentage of subjects with ≥ 4-fold increase in titers from the baseline. GMT ratio is defined as geometric mean of fold increase of post-vaccination titers over the baseline titers. 2. Antigen specific immunoglobulins in terms of GMT, SCR and GMT ratio at Visit 4, 5, 7, 8, 9 and 10. 3. Antigen specific cellular immune responses as determined by interferon-gamma (IFN-γ) ELISpot, interleukin (IL)-4 ELISpot at Visit 8 and 10. 4. Antigen specific cellular immune responses as determined by multi-parameter intracellular cytokine staining (including CD3, CD4, CD8, IFN-γ, IL-2 and IL-4, etc.) flow cytometry at Visit 8 and 10. 5. Safety of MVC-COV1901 in terms of other adverse events, AESI and SAEs within the study period.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase I prospective, open-labeled, single-center study to evaluate the safety and immunogenicity of MVC-COV1901.

This study is a dose escalation study with three separate sub-phases for subjects ≥20 and <50 years of age. Each sub-phase will consist of 15 subjects. Each subject is to complete at least one vaccination.

Phase 1a: 4 sentinel subjects will be recruited to receive 5 mcg S-protein with adjuvant MVC-COV1901 to evaluate preliminary safety data of the vaccine. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1a, dosing of the remaining subjects in Phase 1a and Phase 1b will proceed.

Phase 1b: Another 4 sentinel subjects will be enrolled to receive 15 mcg S-protein with adjuvant MVC-COV1901 in Phase1b. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1b, dosing of the remaining subjects in Phase 1b and Phase 1c will proceed.

Phase 1c: Another 4 sentinel subjects will be enrolled to receive 25 mcg S-protein with adjuvant MVC-COV1901. If no ≥ Grade 3 AE or SAE occurs within 7 days after the first vaccination in the 4 sentinel subjects in Phase 1c, dosing of the remaining subjects in Phase 1c will proceed.

If any ≥ Grade 3 AE or SAE occurs, DSMB will evaluate preliminary safety data and determine if it remains acceptable to continue dosing.

The vaccination schedule consists of two doses of MVC-COV1901 for each study subject, administered by intramuscular (IM) injection 0.5mL in the deltoid region of non-dominant arm preferably 28 days apart, on Day 1 and Day 29. Solicited adverse events (AE) during the 7 day follow up period; unsolicited AEs and laboratory assessment for safety during the 28 day follow up period after each vaccination will be carried out for all study subjects. AEs other than solicited and unsolicited AE, AESI and SAEs will be collected throughout the study period. Immunogenicity response, against SARS-CoV-2, will be assessed on pre-vaccination, 14 days, 28 days after each vaccination and 90 days and 180 days after the last vaccination (Day 1, 15, 29, 43, 57, 119 and 209).

An interim analysis of immunogenicity data for at least the sentinel subjects in each sub-phase (total 12 subjects) and safety data from baseline to 28 days after second vaccination for all subjects will be carried out when all the subjects complete V8 (28 days after the second vaccination).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This prospective Phase I study is designed to be open-labeled to assess the safety and immunogenicity of MVC-COV1901. Open-labeled design is considered acceptable as the primary endpoint is the safety of MVC-COV1901 administration.

4.3 JUSTIFICATION FOR DOSE

As human response to MVC-COV1901 is unknown, this study aims to assess the safety and immunogenicity of the vaccine.

4.4 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all procedures of the study including the last visit or the last scheduled procedure in the Schedule of Activities (SoA), Section 1.3. The study is considered completed when all subjects are no longer being examined or the last study visit or procedure shown in the SoA of all subjects of all study sites have be performed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Male or female healthy volunteer ≥20 and <50 years of age
2. Subject free of ongoing acute diseases or serious medical conditions (e.g. concomitant illness) such as cardiovascular (e.g. New York Heart Association grade III or IV), hepatic (e.g. Child-Pugh Class C), psychiatric condition (e.g. alcoholism, drug abuse), medical history, physical findings, or laboratory abnormality that in the investigator's opinion could interfere with the results of the trial or adversely affect the safety of the subject
3. Female subject must be:
   - Either of non-childbearing potential, i.e. surgically sterilized (defined as having undergone hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy; tubal ligation alone is not considered sufficient) or one year post-menopausal;
     - Or, if of childbearing potential, must be abstinent or agree to use medically effective contraception from 14 days before screening to 30 days following last injection of study vaccines. Acceptable forms include:
       - ✓ Implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)
       - ✓ Established use of hormonal methods (injectable, pill, patch or ring) combined with barrier methods of contraception: condom, or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
   - Have a negative pregnancy test
4. Subject is willing and able to comply with all required study visits and follow-up required by this protocol
5. Subject has no overseas travel within 14 days of screening and will not have any throughout the study period
6. Subject must provide written informed consent or the Subject's legal representative must understand and consent to the procedure

5.2 EXCLUSION CRITERIA

Any subject meeting any of the exclusion criteria will be excluded from study participation:

1. Receiving any investigational intervention either currently or within 30 days of first dose;
2. Subject (particularly who is a healthcare worker) with previous known or potential exposure to SARS CoV-1 or 2 viruses (**EXCEPT** for those who have been tested negative and the 14-days self-managements/ home quarantines/ home isolations are completed), or received any other COVID-19 vaccine;
3. Administration of any vaccine 4 weeks of first dose;
4. A BMI greater than or equal to 30 kg/m^2;
5. Subject with a history of hypersensitivity to any vaccine or a history of allergic disease or reactions likely to be exacerbated by any component of the MVC-COV1901;
6. Administration of any blood product or intravenous immunoglobulin administration within 12 weeks of first dose;

7. Pregnancy or breast feeding or have plans to become pregnant in 30 days after last injection of study vaccines;
8. History of positive serologic test for HIV, hepatitis B surface antigen (HBsAg) or any potentially communicable infectious disease as determined by the investigator or Medical Monitor;
9. Positive serologic test for hepatitis C (**EXCEPTION**: successful treatment with confirmation of sustained virologic response);
10. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 mg/dL;
11. Screening laboratory tests with Grade 2 or higher abnormality (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007);
12. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;
13. A history of autoimmune disease (systemic lupus, rheumatoid arthritis, scleroderma, polyarthritis, thyroiditis, etc.);
14. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or less than prednisone 20 mg/day or equivalent) within 12 weeks of first dose;
15. Current or anticipated treatment with TNF-α inhibitors, e.g. infliximab, adalimumab, etanercept within 12 weeks of first dose;
16. Prior major surgery or any radiation therapy within 12 weeks of first dose;
17. Alcohol or drug abuse or dependence, psychiatric, addictive, or any disorder that, in the opinion of the investigator, would interfere with adherence to study requirements or assessment of immunologic endpoints; or any illness or condition that in the opinion of the investigator may affect the safety of the participant or the evaluation of any study endpoint;
18. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition, tattoos or wound covering the injection site area.
19. Body (oral, rectal or ear) temperature ≥ 38.0°C or acute illness within 2 days of first dose; or acute respiratory illness within 14 days of first dose.
20. Screening laboratory test of antinuclear antibody (ANA), anti-dsDNA antibody, anti-neutrophil cytoplasmic antibodies (ANCA, including cytoplasmic ANCA (c-ANCA), perinuclear ANCA (p-ANCA)) with the value higher than upper normal limit.
21. Abnormal screening electrocardiography (ECG) with clinically significant findings as reviewed by investigator.

5.3 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate this trial but do not meet all the criteria for participation in this trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the regulatory authority requirement and to respond to queries from regulatory authorities and IRBs/IECs. Minimal information includes demographics, and screen failure details.

Subjects who are screen failures are not allowed to be re-screened.

5.4 ELIMINATION CRITERIA

The following elimination criteria should be checked at each visit subsequent to first vaccination. If any become applicable during the study, the subject will not receive further doses of vaccine, and it may not require withdrawal of the subject from the study. The subject's evaluability in the per protocol (PP) analysis may be determined by sponsor.

- Administration of prohibited medication/treatment
- Confirmed COVID-19 infection by available medical records or confirmed definition of Taiwan CDC
- Any pathological event, clinical adverse event, or any change in the subject's status giving indication to the investigator that further vaccination of investigational product may not be the best interest of the subject
- Pregnancy
- Any vaccine-related SAE during the study period

5.5 CONTRAINDICATION TO VACCINATION

The following criteria should be checked prior to each vaccination and subjects who meet criteria at the time scheduled for vaccination may reschedule another date for vaccination upon agreement of investigator, or withdrawn at the discretion of the investigator.

1. Body (oral, rectal or ear) temperature ≥38.0°C or acute illness within 2 days before vaccination
2. Any inactivated vaccine use within 7 days of vaccination visit
3. Any live-attenuated vaccine use within 28 days of vaccination visit
4. Any condition that is a contraindication to vaccination based on the judgement of investigator

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Investigational Product (MVC-COV1901):

MVC-COV1901 is bioreactor derived, and is formulated in the different dosages of Spike (S) protein (5, 15, and 25 mcg) with [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant per dose (0.5mL) supplied in pre-filled syringes in 0.5 mL buffer solution. The recombinant S-2P protein is produced in cells and purified before formulation with CpG 1018 and aluminum hydroxide. CpG 1018 and aluminum hydroxide are adjuvants that enhance immune response.

6.1.2 DOSING AND ADMINISTRATION

Dosing

Investigational Product (MVC-COV1901):

Two doses of 5, 15, or 25 mcg S protein with [redacted] mcg CpG 1018 and aluminum [redacted] mcg in the form of aluminum hydroxide as adjuvant, 28 days apart.

Administration

The administration of MVC-COV1901 will be through intramuscular injection. The local skin will be sterilized before injection. After the intramuscular injection, subject will be observed for at least 1 hour (2 hours for the first 4 subjects at V2) for any immediate adverse reactions, including administration site events (pain, erythema/redness and induration/swelling) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea). Vital signs including blood pressure, respiratory rate, pulse/heart rate, and body temperature will be checked approximately 1 hour after vaccination.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The sponsor is responsible for supplying the investigator(s)/study site(s) with the investigational products (IP). The investigational product must not be used for purposes other than those for this trial, and the clinical trial pharmacist or designated qualified personnel must record the quantity of IP supplied/returned by/to the sponsor to maintain clear drug inventory control. The quantity of investigational product (IP) given to the site and to the subject will be recorded accordingly.

The investigator designated qualified personnel must retain all returned IP until the study monitor has confirmed accountability data and the sponsor has given instruction for the final handling of the IP. Any discrepancy noted will be investigated, resolved, and documented prior to returning or destruction of unused study drug. Unused IP should be returned to the sponsor for destruction or be destroyed at the study site according to standard institutional procedures after drug accountability has been conducted by the sponsor or representative.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Investigational Product (MVC-COV1901):

MVC-COV1901 used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person from the sponsor with Standard Operating Procedures (SOPs) of sponsor, PIC/S GMP guidelines, ICH GCP guidelines, and applicable local laws/regulations. The product will be labeled with descriptions of "Clinical trial use only" as well as other required information according to the local regulatory requirements in the local language.

6.2.3 PRODUCT STORAGE AND STABILITY

Investigational Product (MVC-COV1901):

The MVC-COV1901 should be stored at 2~8°C and protected from light. Each batch shipped, used, and returned from/to the sponsor to/from the clinical site will be recorded according to time and date to keep track of the IP with precise details.

6.2.4 PREPARATION

The final product is supplied readily for use when provided by the sponsor to the study sites. There is no further preparation needed before administration.

6.3 STUDY INTERVENTION COMPLIANCE

The study monitor will assure the subject's compliance with the study protocol. All subjects are to receive two dose administrations on site. The number of vaccinations will be recorded.

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This study will be designed as open-labeled manner, thus no randomization nor blinding will be performed.

6.5 CONCOMITANT THERAPY/MEDICATION

Concomitant therapy is defined as any therapy including surgeries, vaccines, prescriptions, or over the counter medications. Subjects are allowed to receive routinely used medications or treatments for other indications which is judged by the investigator as not affecting the immunogenicity and safety assessments of this study. All therapies taken by the subject prior to the screening and during the study will be recorded on the appropriate page of the CRF/eCRF. Therapies will be categorized as follows:

- Vaccines of any kind: recorded from 4 weeks before first vaccination until EOS
- Immunoglobulins and/or other blood products: recorded from 12 weeks before first vaccination until EOS
- Systemic steroids or other immune-modifying agents: recorded from 12 weeks before first vaccination until EOS
- Major surgeries: recorded within 5 years of first vaccination until EOS

- Radiation therapy: recorded within 5 years before first vaccination until EOS
- All other medications: will be recorded up to 6 weeks before first vaccination until EOS

This record will include the name of the therapy, frequency, unit dose, routes, dates of the drug is started and stopped (if medication/therapy is not ongoing), and the indication for the use of the drug.

6.6 PROHIBITED THERAPY/MEDICATION

The following therapies are prohibited during the study:

- Major surgery or any radiation therapy within 12 weeks of first dose and during the study
- Immunoglobulins and/or other blood products within 12 weeks of first dose and during the study
- Immunosuppressant (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or less than prednisone 20 mg/day or equivalent) within 12 weeks of first dose and during the study
- TNF-α inhibitors including infliximab, adalimumab, etanercept within 12 weeks of first dose and during the study
- Any other investigational intervention within 30 days of first dose and during the study
- Administration of any licensed live attenuated vaccine within 28 days before or after each study vaccination
- Administration of any licensed inactivated vaccine within 7 days before or after each study vaccination

7 SUBJECT WITHDRAWAL

7.1 SUBJECT WITHDRAWAL FROM THE STUDY

Subjects may withdraw voluntarily or involuntarily from the trial due to any of the following conditions:

1. The subject voluntarily decides to withdraw her/his consent
2. The subject dies or is lost to follow-up
3. Non-compliance with the study drug or study schedule
4. Any pathological event, clinical adverse event, laboratory abnormality, intercurrent illness, or any occurrence or change in the subject's status giving indication to the investigator or sponsor that further participation in the study may not be the best interest of the subject
5. The study is terminated prematurely by the investigator, research institution, sponsor, IRB/IEC or regulatory authorities
6. Other reasons to be specified on CRF/eCRF

The reason for early termination must be recorded. If a subject is discontinued due to an AE, every effort will be made to follow the event until event resolves or stabilizes at a level acceptable to the investigator. For subjects who withdraw voluntarily, the study personnel will try to contact the subject to obtain further safety information and to inform them of any significant findings which may affect their safety or health, unless the subject specifies that they do not want to be contacted again.

Biologic samples collected from the subject prior to his or her withdrawal may be used as indicated in the protocol, unless the subject specifies a wish that the samples are to be destroyed.

7.2 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for any scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within time window and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS (IMMUNOGENICITY TEST)

Currently, no correlates of immunity against SARS-CoV-2 have been identified. We speculate that antibody-mediated humoral response as well as cellular T cell response will be activated for protection against infection (Zhou and Zhao, 2020).

Blood samples will be collected at Visit 2 (Day 1) before vaccination, Visit 4 (Day 15), Visit 5 (Day 29) before vaccination, Visit 7 (Day 43), V8 (D57), V9 (D119) and V10 (D209) for antibody and/or T cell response measurement. Serum will be separated and sent for analysis for humoral response, and whole blood will be processed to obtain peripheral blood mononuclear cells to determine cell mediated markers. Neutralizing antibody titers against SARS-CoV-2 S protein will be measured via neutralizing assay. Antigen specific antibody will be measured via ELISA. Antigen specific cellular immune response will be determined by interferon gamma (IFN-γ) ELISpot, interleukin (IL)-4 ELISpot, as well as multi-parameter intracellular cytokine staining flow cytometry (including CD3, CD4, CD8, IFN-γ, IL-2 and IL-4, etc.).

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 INFORM CONSENT

The investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks involved, and any predicted discomforts. Each subject will be informed that participation in the study is voluntary and that he/she can withdraw their participation at any time.

All subjects must provide signed and dated informed consent prior to any study-related procedures. Only the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and the applicable regulatory authorities approved ICF can be used.

8.2.2 SCREENING, ELIGIBILITY, AND ENROLLMENT

Screening is defined as the process for identifying a candidate for the study and evaluating their eligibility to participate. Eligibility should be thoroughly checked by the investigators at Screening Visit and at first Vaccination Visits before vaccination based on the inclusion and exclusion criteria. A subject is recognized as enrolled into the study if this subject consented and is screened, with eligibility verified.

Procedures at Screening Visit must be conducted within 28 days prior to the first Vaccination Visit.

8.2.3 DEMOGRAPHICS

Demographic data, including the subject’s age, birth month, birth year, race, and gender, will be recorded at Screening Visit.

8.2.4 MEDICAL HISTORY

General medical history within 12 weeks before vaccination should be recorded at Screening and the first Vaccination Visit. Serious medical conditions, including cardiovascular, hepatic, psychiatric condition, medical history, physical findings, or laboratory abnormality within 2 years should be recorded. History of malignancy and major surgery, and inflammatory or degenerative neurological disease will be recorded within 5 years of enrollment. All history recorded will include date of onset, diagnosis and current status.

8.2.5 PHYSICAL EXAMINATION, HEIGHT AND WEIGHT

Height and weight will be collected at Screening Visit.

Physical examination will be performed at Visit 1, 2, 4, 5, 7, 8, 9 and 10. Physical examination conducted in this study will include general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, etc. Full physical examination will be performed at Visit 1, 2, 4, 5 and 7. Targeted examinations determined by Investigator or by subject complaints will be performed at V8, V9 and 10. Abnormalities in physical examinations will be evaluated by the investigators and noted as "non-clinical significant (NCS)" or "clinical significant (CS)".

8.2.6 ELECTROCARDIOGRAPHY (ECG)

ECG will be performed at Screening Visit, Visit 2, Visit 4, Visit 5, Visit 7 and Visit 10 for all participants. For Vaccination Visit, ECG will be performed before as well as approximately 1 hour after vaccination. The ECG should include measurements of ventricular rate, P wave, QRS complex, ST segment, T-wave, PR interval, QT interval, with assessment as to whether the ECG is normal or abnormal. Abnormal ECGs will be interpreted as clinically significant or not clinically significant.

8.2.7 VITAL SIGNS

Vital signs will be performed at Screening, and at both Vaccination Visits before as well as approximately 1 hour after vaccination. Vital signs measurement will consist of systolic/diastolic blood pressure, respiratory rate, pulse rate or heart rate, and body temperature. Respiratory rate, pulse/heart rate and blood pressure (systolic/diastolic) will be obtained after the subject has been at rest for at least 5 minutes in a sitting position.

8.2.8 HEMATOLOGY, BIOCHEMISTRY AND IMMUNOLOGY TESTS

Tests to be measured in this study will consist of the followings:

- **Hematology**: Hemoglobin, red blood cells (RBC), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cells (WBC), differential of leukocytes, platelets, prothrombin time (PT) and activated partial thromboplastin time (APTT)
- **Biochemistry**: Sodium (Na), potassium (K), chloride (Cl), fasting glucose, blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine phosphokinase (CPK)

- **Immunology**: ANA, anti-dsDNA antibody, ANCA(c-ANCA and p-ANCA)

Hematology, biochemistry and immunology tests will be performed at Screening, Visit 4, 5, 7, and 8.

8.2.9 PREGNANCY TEST

Urine pregnancy tests will be performed for applicable female subjects at Visit 1, 2, and 5.

8.2.10 SEROLOGY TEST

Serology tests for HIV-1 and HIV-2 (antibody or rapid test), HBV (HBsAg), and HCV antibody will be performed at Screening Visit.

8.2.11 SOLICITED ADVERSE EVENT AND UNSOLICITED ADVERSE EVENT

All adverse events (AEs) will be recorded from vaccination until Visit 10 (EOS).

Solicited adverse events are defined as the adverse events listed below that occurred in 7 days after vaccination

- **Local events**: pain, erythema/redness and induration/swelling
- **Systemic events**: fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea

Unsolicited adverse events are defined as any untoward medical events other than solicited AEs that occurred within 28 days after vaccination.

Other adverse events are defined as any untoward medical events other than solicited AEs and unsolicited AEs.

An AE diary card will be dispended to each subject at Vaccination Visit for recording the AE. Subject should record all AE occurred after vaccination until the next Safety Visit in the diary and return the diary at that visit.

8.3 STUDY SCHEDULE

The assessments or procedures to be performed at each study visit are listed below. The results of protocol specific assessments and procedures will be recorded in the source documents for all study subjects and on the appropriate page of the CRF/eCRF.

Unscheduled visit will be arranged when investigator considers necessary.

8.3.1 SCREENING VISIT (VISIT 1)

The Screening Visit should be scheduled within 28 days before First Vaccination Visit (Day -28 ~ -1).

- Obtain signed informed consent
- Assign identifier number
- Demographics
- Medical history
- Physical examination

- Height and weight
- ECG
- Pregnancy test for applicable subjects
- Vital Signs
- Serology tests (HIV-1 and HIV-2 antibody or rapid test, HBs Ag, HCV antibody)
- Hematology, biochemistry and immunology tests
- Eligibility (inclusion/exclusion criteria)
- Concomitant therapy (as Medication history prior to vaccination)

8.3.2 FIRST VACCINATION VISIT (VISIT 2)

The day of First Vaccination Visit is set as Day 1.

Procedures to be performed before vaccination:
- Medical history
- Concomitant therapy (as Medication history prior to vaccination)
- Physical examination
- Pregnancy test for applicable subjects
- Vital signs
- ECG
- Eligibility (inclusion/exclusion criteria)
- Immunogenicity test
- Contraindication to vaccination

Vaccination:
- Intramuscular injection of MVC-COV1901

Procedures to be performed after Vaccination
- Vital signs (approximately 1 hour after vaccination)
- ECG (approximately 1 hour after vaccination)
- Distribution of diary cards
- AE/SAE collection

8.3.3 EVALUATION VISIT BY PHONE (VISIT 3)

Visit 3 will be performed on Day 8 (±2) by phone call.
- Concomitant therapy
- AE/SAE collection
- Elimination criteria check

8.3.4 SAFETY AND IMMUNOGENICITY TEST VISIT (VISIT 4)

Visit 4 will be performed on Day 15 (±3).
- Concomitant therapy
- AE/SAE collection
- Review returned diary cards
- Physical examination
- Hematology, biochemistry and immunology tests
- ECG

- Elimination criteria check
- Immunogenicity test (humoral immune response only)

8.3.5 SECOND VACCINATION VISIT (VISIT 5)

Visit 5 will be performed on Day 29 (±3).

Procedures to be performed before vaccination:
- Concomitant therapy
- AE/SAE collection
- Physical examination
- Pregnancy test for applicable subjects
- Hematology, biochemistry and immunology tests
- Vital signs
- ECG
- Elimination criteria check
- Immunogenicity test (humoral immune response only)
- Contraindication to vaccination

Vaccination:
- Intramuscular injection of MVC-COV1901

Procedures to be performed after Vaccination
- Vital signs (approximately 1 hour after vaccination)
- ECG (approximately 1 hour after vaccination)
- Distribution of diary cards
- AE/SAE collection

8.3.6 EVALUATION VISIT BY PHONE (VISIT 6)

Visit 6 will be performed on Day 36 (7±2 days after V5) by phone call.
- Concomitant therapy
- AE/SAE collection
- Elimination criteria check

8.3.7 SAFETY AND IMMUNOGENICITY VISIT (VISIT 7)

Visit 7 will be performed on Day 43 (14±3 days after V5).
- Concomitant therapy
- AE/SAE collection
- Review returned diary cards
- Physical examination, Hematology, biochemistry and immunology tests
- ECG
- Elimination criteria check
- Immunogenicity test (humoral immune response only)

8.3.8 IMMUNOGENICITY TEST VISIT (VISIT 8)

Immunogenicity visit will be performed on Day 57 (28±3 days after V5).

- Concomitant therapy
- AE/SAE collection
- Physical examination
- Hematology, biochemistry and immunology tests
- Immunogenicity test
- Elimination criteria check

8.3.9 IMMUNOGENICITY TEST VISIT (VISIT 9)

Immunogenicity visit will be performed on Day 119 (90±7 days after V5).

- Concomitant therapy
- AE/SAE collection
- Physical examination
- Immunogenicity test
- Elimination criteria check

8.3.10 END OF STUDY VISIT (VISIT 10)

Visit 10 will be performed on Day 209 (180±14 days after V5).

- Concomitant therapy
- AE/SAE collection
- Physical examination
- ECG
- Immunogenicity test
- Elimination criteria check
- Study completion check

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Based on ICH GCP, adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or intervention and which does not necessarily have a causal relationship with this vaccination. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product/intervention, whether or not related to the medicinal (investigational) product/intervention.

Solicited AEs are defined as administration site events (pain, erythema/redness and induration/swelling) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea) that occurred in 7 days after vaccination.

Unsolicited AEs are defined as any untoward medical events other than solicited AEs that occurred in 28 days after vaccination.

Other AEs are defined as any untoward medical events other than solicited AEs and unsolicited AEs.

8.4.2 DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

According to Council for International Organizations of Medical Sciences (CIOMS) VII, "*an adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.*"

The AESIs relevant to COVID-19 are shown in following table:

Severe pneumonia	Adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air
Acute respiratory distress syndrome (ARDS)	Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. Oxygenation impairment in adults: • Mild ARDS: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O). • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O). • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O). **If altitude is higher than 1000m, then the correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.* ***When PaO_2 is not available, SpO_2/FiO_2 ≤ 315 suggests ARDS (including in non-ventilated patients)*
Sepsis	Acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.
Septic shock	Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L.
Coagulation disorder	Including but not limited to hemorrhagic disease, idiopathic thrombocytopenia purpura, etc.
Abbreviations: CPAP: continuous positive airway pressure; CT: computed tomography; FiO_2: fraction of inspiration O_2; MAP: mean arterial pressure; PaO_2: partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; SpO_2: oxygen saturation	

8.4.3 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes (based on ICH GCP):

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

8.4.4 CLASSIFICATION OF AN ADVERSE EVENT

8.4.4.1 Severity of Event

All AEs will be assessed for severity by the study investigator using the following guideline *"Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"* (FDA, 2007):

Solicited Adverse Events				
Local Events	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life threatening)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever for > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/ Redness*	2.5 ~ 5 cm	5.1 ~ 10 cm	> 10 cm	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	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. ‡ Grade 0 will be recorded for Erythema/Redness, or Induration/Swelling < 2.5 cm. # The definition of activity in grade 2 refers to work or productive activities. ¥ The definition of daily activity in grade 3 refers to activities of daily living (ADLs): eating, bathing, getting dressed, toileting, transferring, and continence.				
Systemic Events	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life threatening)**
Fever (°C)	38.0 ~ 38.4	38.5 ~ 38.9	39.0 ~ 40.0	> 40.0
Malaise/fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	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
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	ER visit or hospitalization for hypotensive shock
Diarrhea	2~3 loose stools or <400 g/24 hours	4~5 stools or 400~800 g/24 hours	6 or more watery stools or >800 g/24 hours	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Adverse Events other than Solicited Adverse Events				
Systemic Illness	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life threatening)**
Illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
‡ Medical intervention is defined as use of any therapy intended to change the natural outcome of an event, e.g. use of antibiotics to treat infection, other etiological treatment instead of symptomatic relief. # The definition of activity in grade 2 refers to work or productive activities. ¥ The definition of daily activity in grade 3 refers to activities of daily living (ADLs): eating, bathing, getting dressed, toileting, transferring, and continence.				

In case of death, the severity grading will be put as Grade 5.

8.4.4.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study product assessed by the investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The investigator is to determine if the particular AE is related to the study vaccine. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly/Potentially Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the investigational product) and in which other drugs or chemicals or underlying disease

provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- Not related: The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigator.

8.4.5 ADVERSE EVENT REPORTING

AEs may be volunteered spontaneously by the study subject, discovered as a result of general questioning by the study staff, or determined by physical examination and laboratory data. All AEs will be recorded on the CRF. For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. AE will be followed-up until satisfactory resolution or until the site investigator deems the event to be chronic or the subject is stable.

8.4.6 ADVERSE EVENT OF SPECIAL INTEREST REPORTING

The investigator will report to the sponsor/CRO contact any AESI within 24 hours of the investigator's knowledge of the event, regardless of the expectedness and causality to the study intervention. Other supporting documentation of the event may be requested by sponsor and should be provided as soon as possible. If the AESI is also a SAE, reporting should follow the process of SAE reporting as described in Section 8.4.7 and marks it as an AESI in the SAE/AESI reporting form.

8.4.7 SERIOUS ADVERSE EVENT REPORTING

The investigator will report to the sponsor/CRO contact any SAE within 24 hours of the investigator's knowledge of the event, regardless of the expectedness and causality to the study intervention. The reporting of the SAE to the regulatory authorities/IEC/IRB will comply with the local regulations and requirements.

Nevertheless, the following events will not be reported as a SAE:

- Hospitalization due to social reasons in absence of an adverse event
- Hospitalization due to surgery or procedure planned before entry into the study (must be documented in the CRF)

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by sponsor and should be provided as soon as possible.

The sponsor/CRO will be responsible for notifying the regulatory authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after first acknowledged by the Sponsor. A complete report should be provided within 15 calendars by sponsor's acknowledgement and must include an assessment of the importance and implication of the findings and/or previous experience on the same or similar medical products.

Serious, unexpected suspected adverse reactions (SUSARs) is a serious adverse reaction for which a reasonable causal relationship with the investigational product is suspected but not confirmed. SUSARs that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that a case qualifies.

8.4.8 REPORTING OF PREGNANCY

Pregnancy is not considered to be an AE or SAE but any pregnancy complication should be recorded as AE or SAE. However, the investigator must collect pregnancy information of any female subject who become pregnant from vaccination until the end of the study. The investigator must also ensure that any pregnancy is followed up until outcome to detect any congenital anomalies or birth defects.

The pregnancy should be reported to Sponsor and the obstetrician/gynecologist of the subject should be notified for the trial information. Any events (including congenital anomalies/birth defects) that meet the definition of a SAE would need to be notified to Sponsor as per Section 8.4.5. A congenital anomaly will only need to be expedited to competent authorities and IEC/IRB if it met the definition of a serious unexpected suspected adverse reactions. Reporting of pregnancy cases to the regulatory authorities and IRBs/IECs will follow the local regulations.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There is no statistical hypothesis in this study. Descriptive statistics will be presented for all variables defined herein.

9.2 SAMPLE SIZE DETERMINATION

The target sample size is 45 subjects. This is arbitrary and not derived from statistical estimation method.

9.3 POPULATIONS FOR ANALYSES

The following populations will be introduced for statistical analysis for each cohort.

Intend-to-treat (ITT) population:

- All subjects who received at least 1 dose of MVC-COV1901 and for whom data are available

Per-protocol Safety (PPS) population for Analysis of Safety:

- A subset of ITT population
- With at least one safety follow up
- Not received any prohibited vaccine/medications before Visit 8 (Day 57)

Per-protocol (PP) population for Analysis of Immunogenicity:

- Received successfully 2 doses of MVC-COV1901 as assigned
- Fulfill all inclusion and exclusion criteria
- Not met elimination criteria which may interfere a subject's evaluability
- With immunogenicity data at V8 (Day 57)

Analysis of demographic and baseline characteristics will be performed on ITT population, of safety will be on ITT and PPS population (PPS for data up to Visit 8 only), of immunogenicity will be on ITT and PP population. The main conclusion will be made on ITT population analysis results for safety, and PP population results for immunogenicity. The results based on PPS population for safety and ITT for immunogenicity will be performed to complement the analysis.

No procedure for handling missing assessment will be applied.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

There will be a separate formal statistical analysis plan (SAP) to be completed prior to database/data lock. The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies). Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final clinical study report.

All results will be presented using descriptive statistics. Significance tests (2-tailed, alpha=0.05) without alpha adjustment will be performed for pairwise comparison where p-values will be rounded to four decimal places if applied.

Regarding descriptive statistics, continuous variables will be summarized by dosing groups with number of subject, mean, standard deviation, median, range and IQR; while number and percentage of subject for categorical variables. For net change from baseline or fold increase over baseline, 95% confidence interval (CI) of mean and/or median will also be presented.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

1. Safety of MVC-COV1901 in terms of laboratory assessments, the occurrence rate of solicited adverse events, unsolicited adverse events, other AEs, AESI and SAEs within V8 (28 days after second vaccination).

Analyses on laboratory assessments, solicited AE, unsolicited AE, other AEs, AESI and SAEs within V8 (28 days after second vaccination) are described in Safety Analyses section.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

1. Neutralizing titers in terms of geometric mean titer (GMT), seroconversion rate (SCR), and GMT ratio at visit 4, 5, 7, 8, 9 and 10. SCR is defined as the percentage of subjects with ≥ 4-fold increase in titers from the baseline. GMT ratio is defined as geometric mean of fold increase of post-vaccination titers over the baseline titers.

2. Antigen specific immunoglobulin in terms of GMT, SCR, and GMT ratio at visit 4, 5, 7, 8, 9 and 10

   Geometric Mean Titer (GMT)

   GMT is the geometric mean of the antibody titers measured of the grouped subjects. GMT ratio is defined as geometric mean of fold increase of post-vaccination titers over the baseline titers.

   Let X = antibody titer

   GMT (geometric mean titer) = exp {mean of ln(X)},

   GMT ratio = geometric mean of ($X_{post\text{-}vaccination} / X_{baseline}$)

   GMT ratio will also be equal to $GMT_{post\text{-}vaccination} / GMT_{baseline}$
   = exp {mean of $\ln(X_{post\text{-}vaccination})$ – mean of $\ln(X_{baseline})$}

   The GMT and GMT ratio will be presented with two-sided 95% CI. Log-transformed antibody titer, ln(X), will be analyzed by using two-sample t test or Wilcoxon rank-sum test. The CI of GMT and GMT ratio will be calculated by the exponential of CI of the mean ln(X) and the CI of mean ln(X) difference, respectively. In case normality assumption of ln(X) is not valid, additional GMT and GMT ratio and 95% CI estimated from median of ln(X) will also be presented.

Seroconversion Rate (SCR)

SCR is defined as the percentage of subjects with ≥ 4-fold increases from baseline.

Chi-square or Fisher's exact test will be used to pairwise compare the response rates between groups for SCR analysis. 95% CI of the response rate will also be presented.

3. Antigen specific cellular immune responses as determined by interferon-gamma (IFN-γ) ELISPOT, interleukin (IL)-4 ELISPOT at visit 8 and 10

   Antigen specific IFN-γ and IL-4 ELISPOT data, reported in Spot Forming Units per million cells (SFU/10^6 cells), will be summarized by visit and group. Net change from baseline will be compared between groups by using two-sample t test or Wilcoxon rank-sum test with 95% CI presented.

4. Antigen specific cellular immune responses as determined by multi-parameter intracellular cytokine staining (including CD3, CD4, CD8, IFN-γ, IL-2 and IL-4, etc.) flow cytometry at visit 8 and 10

   Antigen specific multi-parameter intracellular cytokine staining flow cytometry data will be summarized by visit and group. Net change from baseline will be compared between groups by using two-sample t test or Wilcoxon rank-sum test with 95% CI presented.

5. Other adverse events, AESI and SAEs within the study period

   Analyses on other AEs, AESI and SAEs are described in Safety Analyses section.

9.4.4 SAFETY ANALYSES

Adverse events will be coded by employing MedDRA. Each AE will be counted once only for a given subject. Severity and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. The information of AEs, such as start date, stop date, severity, relationship, outcome, and duration will be listed by subject and event.

- Solicited AEs will be analyzed by vaccination period (onset in 7 days after 1st or 2nd, 1st, and 2nd vaccination, respectively), reaction type (local / systemic reaction) and event term for each group.
- Unsolicited AEs will be analyzed by vaccination period (onset in 28 days after 1st or 2nd, 1st, 2nd vaccination, respectively), SOC and preferred term for each group.
- Other AEs (onset >28 days after vaccination) will be analyzed by vaccination period (onset > 28 days after 1st or 2nd, 1st, and 2nd vaccination, respectively), SOC and preferred term for each group.
- AESI will be analyzed by vaccination period (onset in 28 days after 1st or 2nd, 1st, and 2nd vaccination, respectively and onset >28 days after 1st and 2nd vaccination, respectively), event term for each group
- SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be analyzed by vaccination period (onset in 28 days after 1st or 2nd, 1st, and 2nd vaccination, respectively, and onset >28 days after 1st and 2nd vaccination, respectively), seriousness criteria, SOC and preferred term for each group.

Abnormalities and clinical significant abnormalities in physical examinations will be summarized by each individual system for each visit. Abnormalities and clinical significant abnormalities in ECG will be summarized by each examination time point. Net changes from pre-vaccination laboratory test results (Visit 4 - Visit 1, Visit 5 – Visit 1, Visit 7 - Visit 5, Visit 8 – Visit 5), and vital signs (1 hour post vaccination – pre vaccination for Visit 2 and 5, respectively) will be analyzed by using two sample t test or Wilcoxon rank-sum test for pairwise comparison.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographics and baseline characteristics will be analyzed by using two sample t test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test as appropriate for pairwise comparison.

9.4.6 PLANNED INTERIM ANALYSES

An interim analysis of immunogenicity data for at least the sentinel subjects in each sub-phases (total 12 subjects) and safety data from baseline to 28 days after second vaccination for all subjects will be carried out when all the subjects complete V8 (28 days after the second vaccination). Data cleaning and statistical analyses detail for interim analyses will be addressed in SAP.

9.4.7 DATA AND SAFETY MONITORING BOARD

If any ≥ Grade 3 AE or SAE occurs during dose escalation, Independent Data and Safety Monitoring Board (DSMB) will meet to determine if it remains acceptable to continue dosing.

Cumulative SAE data will be provided to the DSMB monthly for reviewing. If any vaccine-related SAE occurs, Independent Data and Safety Monitoring Board (DSMB) will meet to oversee ethical and safety aspects of the study conduct. The composition of the DSMB will be outlined in the DSMB Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study intervention. Different Informed Consent Forms (ICFs) subject to regulations and guidelines applicable to clinical studies of local countries and IRB/IEC requirements are submitted to regulatory authorities and IRBs/IECs, respectively, for approval.

In obtaining and documenting informed consent, the investigator must comply with regulations and guidelines applicable to clinical studies of local countries and IRB/IEC requirements and should adhere to International Conference on Harmonization Good Clinical Practice (ICH GCP). Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the subjects. A separate screening consent will not be used for this study. The study consent must be signed prior to conducting study screening procedures.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the subject's study participation. Consent forms will be IRB/IEC-approved and the subject will be asked to read and review the document. The investigator will explain the study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date) and the ICF will be signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to subjects, investigator, the sponsor/CRO and regulatory authorities, whichever is applicable. If the study is prematurely terminated or suspended, the Principal Investigators (PIs) will promptly inform subjects, the IRB/IEC, and sponsor/ contract research organization (CRO), whichever is applicable and will

provide the reason(s) for the termination or suspension. Subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRBs/IECs and/or regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor/CRO. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All activities will be conducted in as private as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, or regulatory authorities may inspect documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, policies of regulatory authorities, or sponsor requirements.

Subject data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the responsible CRO. This will not include the subject's contact or identifying information. Rather, individual subjects and their data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by responsible CRO staff will be secured and password protected.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the responsible CRO. After the study is completed, the archived data will be stored at CRO and transmitted to the sponsor. Future use of the archived data will need the permission of the sponsor. Data will not be removed if the subject is withdrawn.

With the subject's approval and as approved by local IRBs, residue biological samples, if any, will be stored at the sponsor appointed repository complying with regulations and guidelines

applicable to clinical studies of local countries. During the conduct of the study, a subject can choose to withdraw consent to have biological specimens stored for future research. For withdraw subjects, biologic samples collected from the subject prior to his or her withdrawal may be used as indicated in the protocol, unless the subject specifies a wish that the samples are to be destroyed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The name and contact information of the key roles are provided in the following:

- Sponsor: Medigen Vaccine Biologics Corp.
  7F, No. 16, Ln. 120, Sec. 1, Neihu Rd., Taipei City, 114 Taiwan (R.O.C.)
  TEL: +886-2-77450830
- Medical Monitor: Kathy Tai, M.D.
  Associate Medical Director, Medigen Vaccine Biologics Corp.
  7F., No.16, Ln. 120, Sec. 1 Neihu Rd., Taipei 11493, Taiwan
  TEL: +886-2-7745-0830 Ext.604
- CRO: A2 Healthcare Taiwan Corporation
  3F, No. 1, Sec. 4, Renai Rd., Daan District, Taipei City, 106 Taiwan (R.O.C.)
  TEL: +886-2-87736997
- Protocol Author: Vivian Huang, PharmD.
  Medical Writer, A2 Healthcare Taiwan Corporation
  3F, No. 1, Sec. 4, Renai Rd., Daan District, Taipei City, 106 Taiwan (R.O.C.)
  TEL: +886-2-87736997

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the sponsor or an independent medical monitor. The sponsor or medical monitor will evaluate the available safety data after vaccination including but not limited to AEs, physical examinations, vital signs, and available laboratory parameters throughout the study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of subject are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

A separate plan will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A monitoring plan usually focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented on the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the case report form (CRF)/electronic CRF (eCRF) derived from source documents should be consistent with the data recorded on the source documents. Study documents should be retained for a period complying with regulations and guidelines applicable to clinical studies of the local countries. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a period complying with regulations and guidelines applicable to clinical studies of local countries after the last approval of a marketing application and until there are no pending or contemplated marketing applications or until a period complying with regulations and guidelines applicable to clinical studies of local countries have elapsed since the formal discontinuation of clinical development of the study intervention. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP, requirements. The noncompliance may be either on the part of the subject, the investigator, or the

study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations following the regulatory requirements of health authorities and IRB/IEC. All deviations must be sent to the reviewing IRB/IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The data and information associated with this study may be used by sponsor now and in the future for the purposes of presentation, publication at discretion of sponsor or for submission to regulatory agencies. In addition, relative to the release of any proprietary information, sponsor reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the investigator agrees to the release of the data from this study and acknowledges the above publication policy.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11 ABBREVIATIONS

ACE2	Angiotensin Converting Enzyme 2
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANCA	Anti-neutrophil Cytoplasmic Antibodies
ANCA	Anti-neutrophil Cytoplasmic Antibodies
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
c-ANCA	Cytoplasmic ANCA
CD	Cluster of Differentiation
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
Cl	Chloride
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CPK	Creatinine Phosphokinase
Cr	Creatinine
CRF	Case Report Form
CRO	Contact Research Organization
CS	Clinical Significant
CT	Computed Tomography
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiography
eCRF	Electronic Case Report Forms
ELISpot	Enzyme-linked Immune Absorbent Spot
EOS	End of Study
ER	Emergency Room
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GMT	Geometric Mean Titer
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator’s Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
ICTV	International Committee on Taxonomy of Viruses
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
IP	Investigational Product
IQR	Interquartile Range
IRB	Institutional Review Board
ITT	Intention-To-Treat
K	Potassium
LDH	Lactate Dehydrogenase
MAP	Mean Arterial Pressure
Mcg	microgram
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MMR	Measles, Mumps and Rubella
Na	Sodium
NCS	Non-Clinical Significant
p-ANCA	Perinuclear ANCA
PaO_2	Partial Pressure Arterial Oxygen
PEEP	Positive End-Expiratory Pressure
PI	Principle Investigator
PIC/S	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PP	Per Protocol
PPS	Per Protocol Safety
PT	Prothrombin Time
QC	Quality Control
RBC	Red Blood Cells
RBD	Receptor Binding Domain
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome related Coronavirus
SCR	Seroconversion
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation

SUSAR	Serious, Unexpected Suspected Adverse Reactions
TNF-α	Tumor Necrosis Factor-α
WBC	White Blood Cells
WHO	World Health Organization

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13 PROTOCOL AMENDMENT HISTORY

Version	Changes	Rationale
1.0_07Jul2020	NA	Initial protocol
1.1_22Jul2020	1. DSMB will meet if any ≥ Grade 3 AE or SAE occurs during dose escalation and cumulative SAE data will be provided to the DSMB monthly for reviewing 2. ECG will be performed at Screening Visit, Visit 2, Visit 4, Visit 5, Visit 7 and Visit 10 for all participants and for Vaccination Visit, ECG will be performed before as well as approximately 1 hour after vaccination 3. Acceptable forms of medically effective contraception include: ✓ Implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) ✓ Established use of hormonal methods (injectable, pill, patch or ring) combined with barrier methods of contraception: condom, or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/ gel/ film/ cream/ suppository	Per the comments of regulatory authority in Taiwan
	The markers evaluated in cellular immune responses	The markers assessed will be based on relevant updated data
	Typo corrections	Typo correction
1.2_07Sep2020	1. Extend the duration of observation after vaccination to at least 1 hour. 2. Include activated partial thromboplastin time (APTT) in hematology test. 3. Include coagulation disorders in AESIs	Per the comments of regulatory authority in Taiwan
2.0_31Dec2020	Change Visit 9 from Phone Visit to In-person Visit for additional Immunogenicity Test	Modify the form of Visit 9
	Correct the statistical method for antigen specific multi-parameter intracellular cytokine staining flow cytometry	Correct the statistical method
	Update on epidemiology	Update on epidemiology
	Clarify wordings	Clarify wordings