A Phase I/II, Randomized, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of MT-2766 in Japanese Adults

Clinical Study Protocol

Sponsor
Medicago R&D Incorporated

In-Country Clinical Caretaker
Mitsubishi Tanabe Pharma Corporation

Protocol Number: MT-2766-A-101 (CP-PRO-CoVLP-028)
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Confidentiality Statement

This protocol contains information that is to be provided only to persons who are directly involved in the study. The information contained in this document must not be published or disclosed to any third parties without the prior written consents of Mitsubishi Tanabe Pharma Corporation.

This study is to be conducted in compliance with the Pharmaceutical Affairs Law, the Ministerial Ordinance on the Standard for the Conduct of Clinical Studies on Drugs (GCP) and related regulations, and with the protocol.

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Attachment

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Expanded term
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
BMI	body mass index
BP	blood pressure
CI	confidence interval
CMI	cell-mediated immune
CoVLP	Coronavirus-Like Particle
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immuno spot
FDA	Food and Drug Administration
GCP	good clinical practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
IB	Investigator's Brochure
ICCC	In-Country Clinical Caretaker
ICF	informed consent form
IFN	interferon
IgG	immunoglobulin G
IM	intramuscular
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
Medicago	Medicago R&D Incorporated
MTPC	Mitsubishi Tanabe Pharma Corporation
Nab	neutralizing antibody
NHP	non-human primate
OT	oral temperature
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
pIMD	potential immune-mediated disease
PP	per protocol
PR	Pulse rate
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	safety analysis set

SAS®	Statistical Analysis System®
SC	seroconversion
SUSAR	suspected, unexpected serious adverse reaction
Th1	T helper 1
Th2	T helper 2
VAED	vaccine-associated enhanced disease
VLP	virus-like particle
WHO	World Health Organization
US	United States

PROTOCOL SYNOPSIS

Protocol number:	MT-2766-A-101(CP-PRO-CoVLP-028)
Protocol title:	A Phase I/II, Randomized, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of MT-2766 in Japanese Adults
Sponsor:	Medicago R&D Incorporated
In-Country Clinical Caretaker:	Mitsubishi Tanabe Pharma Corporation
Development phase:	Phase I/II
Investigational Medicinal Product:	MT-2766 (Coronavirus-Like Particle COVID-19 vaccine formulated with the AS03 adjuvant at a 1:1 ratio) in a final volume of 0.25 mL or 0.5mL.
Reference product:	Placebo (pH 7.4 phosphate-buffered saline solution containing 0.01 % polysorbate 80) in a final volume of 0.5mL.
Treatment regimen:	Subjects will receive two intramuscular (IM) injections 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once), of one of the following: Group 1: Subjects will receive 3.75 µg of MT-2766 (n = 100) in a final volume of 0.5 mL. Group 2: Subjects will receive placebo for MT-2766 3.75 µg (n = 25) in a final volume of 0.5 mL Group 3: Subjects will receive 1.875 µg of MT-2766 (n = 20) in a final volume of 0.25 mL.
Treatment duration:	Two vaccination separated by 21 days. The planned duration of the study is approximately 14 months, from screening procedures up to the end of the study.
Objectives:	The objective of this study is to evaluate the safety and immunogenicity of MT-2766 in Japanese adults.
Study design:	A randomized, multicenter, observer-blinded, placebo-controlled study with Japanese male and female subjects who are seronegative for SARS-COV-2 antibodies or negative for SARS-COV-2 PCR test at screening. 125 subjects will be randomized 4:1 and will receive the same 3.75 µg of MT-2766 or placebo. Subjects will receive two IM injections 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once), of one of the following blinded treatments: ◆ Group 1: 3.75 µg of MT-2766 in a final volume of 0.5 mL (n=100) ◆ Group 2: Placebo for MT-2766 3.75 µg in a final volume of 0.5 mL (n=25)

	In addition, subjects in Group 3 (n=20) will receive two IM injections of 1.875 µg MT-2766 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once) under open-label. The study may be completed even if fewer than 20 subjects in Group 3 are enrolled. • Group 3: 1.875 µg of MT-2766 in a final volume of 0.25 mL (n=20) Subjects will be screened up to 21 days in advance of the first vaccine administration and will demonstrate a satisfactory baseline medical assessment by history, general physical examination, hematological, biochemical, urinalysis and serological analysis. Although tests for SARS-CoV-2 antibodies and PCR will be performed at screening, negative subjects will be enrolled. On Day 0 and Day 21, vaccine administration will occur. Phone contacts will be made after each vaccine administration, specifically for review of the subject's safety and concomitant medication data. Visits to the study site will occur 3 days after each vaccine administration for key safety assessments, and 21 days after each vaccine administration for key safety and immunogenicity assessments. Subjects will return to the study site on Day 128, Day 201, and Day 386 (3-month, 6-month, and 12-month safety follow-ups and immunogenicity assessments after the last vaccine administration). In Group 1 and Group 2, the randomization code will be opened after data lock when all subjects in Groups 1 and 2 have reached Day 42. Once the study is unblinded, if the efficacy may be inadequate or unconfirmable, public vaccination will be recommended in Group 1 (3.75 µg of MT-2766). Once the study is unblinded, public vaccination will be recommended in Group 2 (placebo group). If subject receives the vaccination, the subject will be withdrawn from the study. In Group 3, if Medicago determines that the efficacy may be inadequate or unconfirmable, all subjects in Group 3 will be recommended to receive public vaccination. If subject receives the vaccination, the subject will be withdrawn from the study.
Planned number of subjects:	145 subjects will be enrolled. Group 1: Subjects will receive 3.75 µg of MT-2766 in a final volume of 0.5 mL (n = 100). Group 2: Subjects will receive placebo in a final volume of 0.5 mL (n = 25). Group 3: Subjects will receive 1.875 µg of MT-2766 in a final

	volume of 0.25 mL (n = 20). The sample size is not based on power calculations but is set to meet the objectives of this clinical study. For Group 3, the study may be completed even if fewer than 20 subjects are enrolled.
Subject population:	Japanese males and females ≥20 years of age
Inclusion criteria:	Subjects must meet all of the following inclusion criteria at the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2) to be eligible for participation in this study. All Investigator assessment-based judgments must be carefully and fully documented in the source documents: 1. Subjects must have read, understood, and signed the informed consent form (ICF) prior to participating in the study; subjects must also complete study-related procedures and must communicate with the study staff at visits and by phone during the study; 2. At the Screening visit (Visit 1), Japanese male and female subjects must be ≥20 years of age; 3. At the Screening visit (Visit 1) and 1st vaccination visit (Visit 2), subject must have a body mass index (BMI) of ≥18.5 kg/m2 and <30 kg/m2; 4. Subjects are considered by the Investigator to be reliable and likely to cooperate with the assessment procedures and be available for the duration of the study; 5. Female subjects of childbearing potential must have a negative serum pregnancy test result at the Screening visit (Visit 1) and a negative urine pregnancy test result at 1st vaccination visit (Visit 2): Non-childbearing females are defined as: ➢ Surgically sterile (defined as bilateral tubal ligation, hysterectomy or bilateral oophorectomy performed more than one month prior to the first study vaccination); OR ➢ Post-menopausal (absence of menses for 12 consecutive months and age consistent with natural cessation of ovulation); 6. Female subjects of childbearing potential must use an effective method of contraception for one month prior to 1st vaccination visit (Visit 2) and agree to continue employing highly effective birth control measures for at least one month

	after the last study vaccination (or in the case of early termination, she must not plan to become pregnant for at least one month after her last study vaccination); 7. Subjects must be non-institutionalized (e.g. not living in rehabilitation centers or old-age homes; subjects who can live independently are acceptable); 8. Subjects have no acute or evolving medical problems prior to study participation and no clinically relevant abnormalities that could jeopardize subject safety or interfere with study assessments, as assessed by the Principal Investigator or sub-Investigator (thereafter referred as Investigator) and determined by medical history, physical examination, serology, clinical chemistry and hematology tests, urinalysis, and vital signs. Investigator discretion is permitted with this inclusion criterion.
Exclusion criteria:	Subjects who meet any of the following exclusion criteria at the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2) will not be eligible for participation in this study. All Investigator assessment-based judgments must be carefully and fully documented in the source documents: 1. According to the Investigator's opinion, significant acute or chronic, uncontrolled medical or neuropsychiatric illness. Acute disease is defined as presence of any moderate or severe acute illness with or without a fever within 48 hours prior to the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2). 'Uncontrolled' is defined as: ➢ Requiring a new medical or surgical treatment during the three months prior to study vaccine administration; ➢ Requiring any significant change in a chronic medication (i.e. drug, dose, frequency) during the three months prior to study vaccine administration due to uncontrolled symptoms or drug toxicity unless the innocuous nature of the medication change meets the criteria outlined in inclusion criterion no. 8 and is appropriately justified by the Investigator. Investigator discretion is permitted with this exclusion criterion. 2. Any confirmed or suspected current immunosuppressive condition or immunodeficiency, including cancer, HIV, hepatitis B or C infection (subjects with a history of cured

	hepatitis B or C infection without any signs of immunodeficiency at present time are allowed). Investigator discretion is permitted with this exclusion criterion; 3. Current autoimmune disease (such as rheumatoid arthritis, systemic lupus erythematosus or multiple sclerosis). Investigator discretion is permitted with this exclusion criterion. Subjects may be eligible to participate with appropriate written justification in the source document. For example, subjects with a history of autoimmune disease who are disease-free without treatment for three years or more, subjects receiving stable thyroid replacement therapy, and subjects with mild psoriasis (i.e. a small number of minor plaques requiring no systemic treatment) are eligible for participation; 4. Administration of any medication or treatment that may alter the vaccine immune responses, such as: ➢ Systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for 10 or more days in total, within one month prior to the 1st vaccination visit (Visit 2). Inhaled, nasal, ophthalmic, dermatological, and other topical glucocorticoids are permitted; ➢ Cytotoxic, antineoplastic, or immunosuppressant drugs - within 36 months prior to 1st vaccination visit (Visit 2); ➢ Any immunoglobulin preparations, blood products, or blood transfusion – within 6 months prior to 1st vaccination visit (Visit 2); 5. Administration of any vaccine within 14 days prior to 1st vaccination visit (Visit 2); planned administration of any vaccine during the study (up to Day 28). Immunization on an emergency basis during the study will be evaluated on case-by-case basis by the Investigator; 6. Administration of any other SARS-CoV-2/COVID-19 vaccine, or other experimental coronavirus vaccine at any time prior to or during the study; 7. At screening (Visit 1), subjects found to be seropositive for SARS-COV-2 infection based on N-protein ELISA or positive for SARS-COV-2 PCR test; 8. Subjects with previous diagnosis of COVID-19 or previous positive SARS-CoV-2 infection; 9. Use of any investigational or non-registered product within 30 days or 5 half-lives, whichever is longer, prior to 1st vaccination visit (Visit 2), or planned use during the study

	period. Subjects who are in a prolonged post-administration observation period of another investigational or marketed drug clinical study, for which there is no ongoing exposure to the investigational or marketed product and all scheduled on-site visits are completed, will be allowed to take part in this study, if all other eligibility criteria are met; 10. Have a rash, dermatological condition, tattoos, muscle mass, or any other abnormalities at injection site that may interfere with injection site reaction rating. Investigator discretion is permitted with this exclusion criterion: 11. Use of any prescription antiviral drugs with the intention of COVID-19 prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have not been licensed for this indication, within one month prior to 1st vaccination visit (Visit 2); 12. Use of prophylactic medications (e.g. antihistamines [H1 receptor antagonists], nonsteroidal anti-inflammatory drugs [NSAIDs], systemic and topical glucocorticoids, non-opioid and opioid analgesics) within 24 hours prior to the 1st vaccination (Visit 2) to prevent or pre-empt symptoms due to vaccination; 13. History of a serious allergic response to any of the constituents of MT-2766; 14. History of a documented anaphylactic reactions to plants or plant components (including tobacco, fruits, and nuts); 15. Personal or family (first-degree relatives) history of narcolepsy; 16. Subjects with a history of Guillain-Barré Syndrome; 17. Any female subject who has a definitely or possibly positive pregnancy test result prior to vaccination or who is lactating; 18. As a result of the medical screening process, the Investigator considers the subject not suitable for the study.
Endpoints:	**Primary Endpoint(s)** The following primary immunogenicity and safety endpoints are for Groups 1 (3.75 μg of MT-2766) and Group 2 (placebo for MT-2766 3.75 μg). **Safety:** 1. The incidences, severity, and investigator-assessed causality of immediate adverse events (AEs) that occur within 30 minutes of first (Day 0) and second (Day 21) injections. 2. The incidences and severity of the following solicited AEs

	that develop within 7 days of first (Day 0) and second (Day 21) injections: (i) local AEs (injection site erythema, injection site swelling, injection site induration, and injection site pain) and (ii) systemic AEs (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck). 3. The incidences, severity, and investigator-assessed causality of unsolicited AEs that develop within 21 days of first (Day 0) and second (Day 21) injections. 4. The incidences of serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and deaths up to 21 days following first (Day 0) and second (Day 21) injections. AESIs include vaccine-associated enhanced diseases (VAED), hypersensitivity reactions, and potential immune-mediated diseases (pIMDs). **Immunogenicity:** 1. SARS-CoV-2 neutralizing antibody (Nab) responses will be analyzed on Days 0, 21, and 42 using the following parameters: geometric mean antibody titer (GMT), seroconversion (SC) rate, and geometric mean fold rise (GMFR); 2. SARS-CoV-2-specific T helper 1 (Th1) CMI responses will be measured on Days 0, 21, and 42 using the interferon (IFN)-γ enzyme-linked immunospot (ELISpot) assay; 3. SARS-CoV-2-specific T helper 2 (Th2) CMI responses will be measured on Days 0, 21, and 42 using the interleukin (IL)-4 ELISpot assay. **Secondary Endpoint(s)** The following secondary safety and immunogenicity endpoints are for Groups 1 and Group 2. **Safety:** 1. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 43 to Day 201; 2. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 202 to Day 386; 3. The numbers and percentages of subjects with normal and abnormal urine, hematological, and biochemical test results within three days of first (Day 0) and second (Day 21) injections.

	Immunogenicity: 1. Persistence of SARS-CoV-2 Nab response will be assessed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR. 2. SARS-CoV-2-specific antibody responses will be measured on Days 0, 21, and 42 based on the total immunoglobulin G (IgG) level, and the persistence of these antibodies will be analyzed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR; 3. SARS-CoV-2-specific Th1 CMI responses will be measured on Days 201 and 386 using the IFN-γ ELISpot assay; 4. SARS-CoV-2-specific Th2 CMI responses will be measured on Days 201 and 386 using the IL-4 ELISpot assay; **Exploratory Endpoint(s)** **Immunogenicity:** 1. For Group 1 and Group 2, SARS-CoV-2-specific CMI responses will be assessed on Days 0, 21, 42, 201, and 386 based on the percentage of CD4+ T cells expressing functional markers. 2. For Group 1 and Group 2, plant glycan–specific antibody responses will be assessed on Days 0, 42, 201 and 386 based on serum IgE levels directed against bromelain-derived cross-reactive carbohydrate determinant MUXF3. 3. For Group 1 and Group 2, Further characterization of the MT-2766–induced immune response, if informative; 4. For Group 3 (1.875 μg of MT-2766), the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed as exploratory endpoints. **Safety** 1. For Group 3, the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed as exploratory endpoints.

1 INTRODUCTION

1.1 Novel Coronavirus Infection

A cluster of pneumonia cases of unknown etiology was identified in the city of Wuhan in Hubei province of China in December 2019. The symptoms included fever, cough, and fatigue, as well as sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. Acute respiratory distress syndrome, acute cardiac injury, and multiple organ failure that led to death were also reported in some cases. The symptoms of the disease were more severe in older age groups with comorbidities, while hypertension, type 2 diabetes, asthma, and chronic obstructive pulmonary disease were also identified as risk factors [Liu 2020a, Yang 2020]. A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was identified as the agent causing the outbreak [Guan 2020]. The disease was subsequently named "novel coronavirus" or COVID-19. The rapidly evolving situation with SARS-CoV-2 infection in China and spread of the disease across many countries prompted the World Health Organization (WHO) to declare a pandemic in March 2020. The presence of many types of SARS-CoV-2 has been reported by multiple groups, showing that the virus has been rapidly mutating during the course of the pandemic.

In Japan, in January 2020, COVID-19 was designated a "specified infectious disease" based on the Infectious Diseases Act and a "quarantinable infectious disease" based on the Quarantine Act. A state of emergency was declared in April 2020 because of the rapid spread of COVID-19 infections since March 2020. Although the number of new infections decreased, with only 21 new cases being reported on May 25, 2020, the day on which the state of emergency was lifted, the number of new cases started to increase again in the first part of July 2021, and the pandemic seems to be accelerating, with more than 2000 new cases in 1 day being reported in the beginning of July 2021. As of now, in August2021, the total number of cases worldwide has exceeded 200 million, and the total number of cases in Japan has exceeded 1,160,000 although, because many cases are asymptomatic or present with only cold-like symptoms, it is thought that there are also many people who have been infected but have not been tested.

1.2 Tests for the Novel Coronavirus

There are two types of tests for COVID-19: tests that detect the presence of the virus, and tests that detect antibodies. According to the "Pathogen Detection Manual – 2019-nCoV" issued by the Japanese National Institute of Infectious Diseases, the presence of the virus is detected using a method such as a polymerase chain reaction (PCR) method that detects the spike protein and open reading frame 1a from the SARS-CoV-2 gene region. It is also possible to determine whether or not a person has been infected in the past by using an antibody test to detect antibodies, such as IgM antibodies and IgG antibodies, which indicate that the person has developed an immune response to the infection.

According to the "Advice for Seeking Advice/Treatment For Infection With the Novel Coronavirus" issued by the Japanese Ministry of Health, Labour and Welfare, the general guidelines for seeking advice and/or treatment is that if a person (1) experiences any severe symptoms such as shortness of breath, intense fatigue, or high fever, (2) has relatively mild cold symptoms, such as a fever and/or cough, but is at risk for becoming seriously ill because of, for example, advanced age or an underlying condition such as diabetes, heart failure or a respiratory

illness, or (3) has relatively mild, but persistent, cold symptoms, such as a fever and/or cough, then the person may need to be tested, at the discretion of a physician.

1.3 Treatments for Infection With the Novel Coronavirus

Pneumonia symptoms classified by level of severity based on oxygen saturation have been the biggest concern with COVID-19. In mild cases, these symptoms often resolve naturally with only course observation, and no special medical care, in moderate to severe cases patients need to be hospitalized for treatment. In addition, in severe cases the patient may need to be treated with inhaled oxygen or put on a ventilator or extracorporeal membrane oxygenation device. The "Guidelines for COVID-19 Drug Therapy, Version 6" compiled by the Japanese Association for Infectious Diseases in August 2020 state that drug therapy should be considered in patients with hypoxemia requiring inhaled oxygen, mechanical ventilation, or ECMO and in patients at high risk of death or the condition becoming more serious.

In Japan, the drug therapies that are currently available for COVID-19 are remdesivir, baricitinib, casirivimab/imdevimab (genetical recombination). Dexamethasone is indicated for severe infections in Japan. Also, in addition to favipiravir, the "Novel Coronavirus Infection (COVID-19) Treatment Guidelines, Version 5.2" also lists adrenomedullin, ivermectin, sarilumab, ciclesonide, tocilizumab, nafamostat, and nelfinavir as drugs for off-label use that can be obtained domestically in Japan. However, because little is currently known about drug therapies for COVID-19, and because there are no drugs that are particularly effective, and symptomatic therapy is the mainstay of treatment, the development of a prophylactic vaccine is considered vital.

1.4 Prophylactic Medications for Novel Coronavirus Infections

The start of 2020 saw the rapid spread of COVID-19 infections, and research institutes and drug manufacturers around the world started working on developing new vaccines, including inactivated vaccines, recombinant protein vaccines, peptide vaccines, messenger RNA vaccines, DNA vaccines, and virus vector vaccines.

1.5 Background of the Investigational Product

MT-2766 consists of virus-like particle (VLP) vaccine for COVID-19 administered in a 1:1 (v:v) ratio with the adjuvant AS03. The vaccine is a plant-derived, VLP vaccine for COVID-19 prophylaxis that is being developed by Medicago Inc. (Medicago), which is a Mitsubishi Tanabe Pharma Corporation group company.

This plant-derived VLP vaccine is made by inserting the genes of the protein shell using the cell of a plant, for example, as the host cell. Medicago used Nicotiana benthamiana to produce VLPs having the SARS-CoV-2 S protein. Medicago has previously used this same platform to manufacture VLP vaccines for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses (not yet NDA or MAA approved by authorities). The S protein is presented on VLPs in a pre-fusion conformation that resembles the native structure of SARS-CoV-2 viruses, which theoretically allows it to be easily recognized by the immune system to induce a neutralizing antibody (Nab) response. Because there is no need to use live

virus in plant-based VLP manufacture, and because no microbial pathogens can infect both plants and humans, the risk of exposure to potentially pathogenic adventitious agents is greatly reduced, resulting in a safety profile that is comparable to or slightly better than what has been reported for other types of vaccines. In addition, Medicago's previous data suggests that plant-made VLP vaccines induce not only antibodies, but also strong CD4+ T cell immunity which may be important for both the persistence of immunity and the provision of better protection.

Medicago has already conducted a phase 1 study of MT-2766 in Canada and confirmed its safety. In addition, the phase 2 part of a phase 2/3 study to confirm efficacy and immunogenicity is currently underway in Canada and the United States (US), and the phase 3 part of the phase 2/3 study to confirm efficacy and safety in disease prophylaxis is currently underway in multiple regions, including North America, Latin America, and Europe.

MT-2766 is a development code named by Mitsubishi Tanabe Pharma Corporation (MTPC) in Japan and the investigational vaccine, Coronavirus-Like Particle (CoVLP), is the same as that manufactured in Medicago's commercial manufacturing site in North Carolina.

1.6 Background of the Adjuvant AS03

The adjuvant AS03 is an established effective adjuvant used in the formulations for Arepanrix™ and Pandemrix™ and is manufactured by GlaxoSmithKline. The AS03-adjuvanted pandemic influenza vaccines have been shown to be more immunogenic than non-adjuvanted vaccines, offering the potential of cross-clade immunity and feasibility of antigen-sparing. High efficacy and effectiveness have been demonstrated for AS03-adjuvanted H1N1 pandemic influenza vaccines in a wide range of populations [Garcon 2012]. Clinical data with AS03-adjuvanted antigen-sparing formulations have shown that immunization against influenza caused by the potential pandemic subtypes H5N1, H1N1, H7N1, H7N9, and H9N2 has demonstrated satisfactory immunogenic potency, as measured by haemagglutinin-inhibition titers, with reduced antigen doses in adults [Baz 2013, Jackson 2015, Lansbury 2017, Leroux-Roels 2007, Madan 2017, Madan 2017a, Madan 2017b, McElhaney 2013, Yang 2013, Yin 2011]. Also, AS03-adjuvanted H5N1 vaccines were shown to induce cross-clade neutralizing antibody responses [Leroux-Roels 2007] and antibody affinity maturation [Khurana 2018].

Data from clinical trials with over 55 000 vaccinated subjects showed that AS03-adjuvanted influenza vaccines exhibited an acceptable safety profile [Cohet 2019, Garcon 2012, Vaughn 2014]. Increased reactogenicity, both local and general, is consistently noted for AS03-adjuvanted vaccines compared with the corresponding unadjuvanted vaccines [Garcon 2012, Launay 2013, Nolan 2014, Waddington 2010]. Most symptoms were mild to moderate in intensity and of short duration. An increased risk of narcolepsy was observed in some individuals after the vaccination campaign with Pandemrix™ in 2009-2010. A similar risk of narcolepsy was not identified with other non-adjuvanted influenza vaccines or other AS03-adjuvanted vaccines, like Arepanrix™ [Montplaisir 2014, Cohet 2015]. Current data suggest that cases of narcolepsy seen immediately following the 2009-2010 pandemic were most likely the result of an immune cascade, triggered by CD4 T cell cross-reactivity to HA proteins from the H1N1 virus itself and hypocretin.

Research is continuing to assess whether either of the main components of the 2009/2010 flu pandemic vaccine (e.g., the viral proteins in the form used in the vaccine or the AS03 adjuvant)

may have contributed to the reaction.

1.7 Non-clinical Studies

For comprehensive preclinical information regarding the safety and toxicity of CoVLP, refer to the current Investigator's Brochure (IB).

1.8 Clinical Studies

Currently, a Phase 1 clinical study (CP-PRO-CoVLP-019) in Canada testing one and two doses of CoVLP at three different dose levels (3.75 µg, 7.5 µg and 15 µg) alone and in combination with two different adjuvants (e.g. AS03, CpG1018) in 180 healthy adults is nearing completion with complete safety data to Day 42 and key Day 42 immunogenicity data available at the time of protocol preparation. Safety data collected to date do not reveal any safety concerns about either CoVLP alone or with either of the two adjuvants at any dose level. The data from this study clearly demonstrate the superiority of AS03 in the induction of anti-SARS-CoV-2 antibodies at all dose levels. These data also suggest that two doses of AS03-adjuvanted CoVLP are needed to achieve consistently high antibody responses in healthy adults since robust boosting in the Day 42 antibody response after two doses of AS03-adjuvanted CoVLP was observed at all dose levels, Medicago has decided to carry the lowest dose, 3.75 µg, and to select AS03 as adjuvant forward into the Phase 2/3 study (CP-PRO-CoVLP-021). The Phase 2/3 study is being conducted in the US, Canada, Europe and South America by Medicago.

1.9 Clinical Study Organizational Structure

Medicago is the Sponsor of this study and Mitsubishi Tanabe Pharma Co. is the In-Country Clinical Caretaker (ICCC) in Japan.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objective

The objective of this study is to evaluate the safety and immunogenicity of MT-2766 in Japanese adults.

2.2 Study Endpoints

2.2.1 Primary Endpoints

The following primary immunogenicity and safety endpoints are for Groups 1 (3.75 μg of MT-2766) and Group 2 (placebo for MT-2766 3.75 μg).

Safety:

1. The incidences, severity, and investigator-assessed causality of immediate adverse events (AEs) that occur within 30 minutes of first (Day 0) and second (Day 21) injections.
2. The incidences and severity of the following solicited AEs that develop within 7 days of first (Day 0) and second (Day 21) injections: (i) local AEs (injection site erythema, injection site swelling, injection site induration, and injection site pain) and (ii) systemic AEs (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck).
3. The incidences, severity, and investigator-assessed causality of unsolicited AEs that develop within 21 days of first (Day 0) and second (Day 21) injections.
4. The incidences of serious AEs (SAEs), medically attended AEs (MAAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and deaths up to 21 days following first (Day 0) and second (Day 21) injections. AESIs include vaccine-associated enhanced diseases (VAED), hypersensitivity reactions, and potential immune-mediated diseases (pIMDs).

Immunogenicity:

1. SARS-CoV-2 neutralizing antibody (Nab) responses will be analyzed on Days 0, 21, and 42 using the following parameters: geometric mean antibody titer (GMT), seroconversion (SC) rate, and geometric mean fold rise (GMFR);
2. SARS-CoV-2-specific T helper 1 (Th1) cell-mediated immune (CMI) responses will be measured on Days 0, 21, and 42 using the interferon (IFN)-γ enzyme-linked immunospot (ELISpot) assay;
3. SARS-CoV-2-specific T helper 2 (Th2) CMI responses will be measured on Days 0, 21, and 42 using the interleukin (IL)-4 ELISpot assay.

2.2.2 Secondary Endpoints

The following secondary safety and immunogenicity endpoints are for Groups 1 and Group 2.

Safety:

1. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 43 to Day 201;
2. The incidences of SAEs, MAAEs, AEs leading to withdrawal, AESIs, and deaths from Day 202 to Day 386;
3. The numbers and percentages of subjects with normal and abnormal urine, hematological, and biochemical test results within three days of first (Day 0) and second (Day 21) injections.

Immunogenicity:

1. Persistence of SARS-CoV-2 Nab response will be assessed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR.
2. SARS-CoV-2-specific antibody responses will be measured on Days 0, 21, and 42 based on the total immunoglobulin G (IgG) level, and the persistence of these antibodies will be analyzed on Days 128, 201, and 386 using the following parameters: GMT, SC rate, and GMFR;
3. SARS-CoV-2-specific Th1 CMI responses will be measured on Days 201 and 386 using the IFN-γ ELISpot assay;
4. SARS-CoV-2-specific Th2 CMI responses will be measured on Days 201 and 386 using the IL-4 ELISpot assay;

2.2.3 Exploratory Endpoints

Immunogenicity:

1. For Group 1 and Group 2, SARS-CoV-2-specific CMI responses will be assessed on Days 0, 21, 42, 201, and 386 based on the percentage of CD4+ T cells expressing functional markers.
2. For Group 1 and Group 2, plant glycan–specific antibody responses will be assessed on Days 0, 42, 201 and 386 based on serum IgE levels directed against bromelain-derived cross-reactive carbohydrate determinant MUXF3.
3. For Group 1 and Group 2, Further characterization of the MT-2766–induced immune response, if informative;
4. For Group 3 (1.875 μg of MT-2766), the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed as exploratory endpoints.

Safety

1. For Group 3, the same analyses as the primary and secondary endpoints in Group 1 and Group 2 will be performed as exploratory endpoints.

3 SUBJECTS

3.1 Subjects

Japanese males and females ≥20 years of age

3.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria at the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2) to be eligible for participation in this study. All Investigator assessment-based judgments must be carefully and fully documented in the source documents:

1. Subjects must have read, understood, and signed the informed consent form (ICF) prior to participating in the study; subjects must also complete study-related procedures and must communicate with the study staff at visits and by phone during the study;
2. At the Screening visit (Visit 1), Japanese male and female subjects must be ≥20 years of age;
3. At the Screening visit (Visit 1) and 1st vaccination visit (Visit 2), subject must have a body mass index (BMI) of ≥18.5 kg/m2 and <30 kg/m^2;
4. Subjects are considered by the Investigator to be reliable and likely to cooperate with the assessment procedures and be available for the duration of the study;
5. Female subjects of childbearing potential must have a negative serum pregnancy test result at the Screening visit (Visit 1) and a negative urine pregnancy test result at 1st vaccination visit (Visit 2):

   Non-childbearing females are defined as:

   - Surgically sterile (defined as bilateral tubal ligation, hysterectomy or bilateral oophorectomy performed more than one month prior to the first study vaccination);

   OR

   - Post-menopausal (absence of menses for 12 consecutive months and age consistent with natural cessation of ovulation);
6. Female subjects of childbearing potential must use an effective method of contraception for one month prior to 1st vaccination visit (Visit 2) and agree to continue employing highly effective birth control measures for at least one month after the last study vaccination (or in the case of early termination, she must not plan to become pregnant for at least one month after her last study vaccination);
7. Subjects must be non-institutionalized (e.g. not living in rehabilitation centers or old-age homes; subjects who can live independently are acceptable);
8. Subjects have no acute or evolving medical problems prior to study participation and no clinically relevant abnormalities that could jeopardize subject safety or interfere with study assessments, as assessed by the Principal Investigator or sub-Investigator (thereafter referred as Investigator) and determined by medical history, physical examination, serology, clinical chemistry and hematology tests, urinalysis, and vital signs. Investigator discretion is permitted with this inclusion criterion.

3.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria at the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2) will not be eligible for participation in this study. All Investigator assessment-based judgments must be carefully and fully documented in the source documents:

1. According to the Investigator's opinion, significant acute or chronic, uncontrolled medical or neuropsychiatric illness.

   Acute disease is defined as presence of any moderate or severe acute illness with or without a fever within 48 hours prior to the Screening visit (Visit 1) and/or 1st vaccination visit (Visit 2).

   'Uncontrolled' is defined as:

   - Requiring a new medical or surgical treatment during the three months prior to study vaccine administration;
   - Requiring any significant change in a chronic medication (i.e. drug, dose, frequency) during the three months prior to study vaccine administration due to uncontrolled symptoms or drug toxicity unless the innocuous nature of the medication change meets the criteria outlined in inclusion criterion no. 8 and is appropriately justified by the Investigator.

   Investigator discretion is permitted with this exclusion criterion.

2. Any confirmed or suspected current immunosuppressive condition or immunodeficiency, including cancer, HIV, hepatitis B or C infection (subjects with a history of cured hepatitis B or C infection without any signs of immunodeficiency at present time are allowed). Investigator discretion is permitted with this exclusion criterion;
3. Current autoimmune disease (such as rheumatoid arthritis, systemic lupus erythematosus or multiple sclerosis). Investigator discretion is permitted with this exclusion criterion. Subjects may be eligible to participate with appropriate written justification in the source document. For example, subjects with a history of autoimmune disease who are disease-free without treatment for three years or more, subjects receiving stable thyroid replacement therapy, and subjects with mild psoriasis (i.e. a small number of minor plaques requiring no systemic treatment) are eligible for participation;
4. Administration of any medication or treatment that may alter the vaccine immune responses, such as:
   - Systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for 10 or more days in total, within one month prior to the 1st vaccination visit (Visit 2). Inhaled, nasal, ophthalmic, dermatological, and other topical glucocorticoids are permitted;
   - Cytotoxic, antineoplastic, or immunosuppressant drugs - within 36 months prior to 1st vaccination visit (Visit 2);
   - Any immunoglobulin preparations, blood products, or blood transfusion – within 6 months prior to 1st vaccination visit (Visit 2);
5. Administration of any vaccine within 14 days prior to 1st vaccination visit (Visit 2); planned administration of any vaccine during the study (up to Day 28). Immunization on

an emergency basis during the study will be evaluated on case-by-case basis by the Investigator;

6. Administration of any other SARS-CoV-2/COVID-19 vaccine, or other experimental coronavirus vaccine at any time prior to or during the study;
7. At screening (Visit 1), subjects found to be seropositive for prior SARS-COV-2 infection based on N-protein ELISA or positive for SARS-COV-2 PCR test;
8. Subjects with previous diagnosis of COVID-19 or previous positive SARS-CoV-2 infection
9. Use of any investigational or non-registered product within 30 days or 5 half-lives, whichever is longer, prior to 1st vaccination visit (Visit 2), or planned use during the study period. Subjects who are in a prolonged post-administration observation period of another investigational or marketed drug clinical study, for which there is no ongoing exposure to the investigational or marketed product and all scheduled on-site visits are completed, will be allowed to take part in this study, if all other eligibility criteria are met;
10. Have a rash, dermatological condition, tattoos, muscle mass, or any other abnormalities at injection site that may interfere with injection site reaction rating. Investigator discretion is permitted with this exclusion criterion:
11. Use of any prescription antiviral drugs with the intention of COVID-19 prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have not been licensed for this indication, within one month prior to 1st vaccination visit (Visit 2);
12. Use of prophylactic medications (e.g. antihistamines [H1 receptor antagonists], nonsteroidal anti-inflammatory drugs [NSAIDs], systemic and topical glucocorticoids, non-opioid and opioid analgesics) within 24 hours prior to the 1st vaccination (Visit 2) to prevent or pre-empt symptoms due to vaccination;
13. History of a serious allergic response to any of the constituents of MT-2766;
14. History of a documented anaphylactic reactions to plants or plant components (including tobacco, fruits, and nuts);
15. Personal or family (first-degree relatives) history of narcolepsy;
16. Subjects with a history of Guillain-Barré Syndrome;
17. Any female subject who has a definitely or possibly positive pregnancy test result prior to vaccination or who is lactating;
18. As a result of the medical screening process, the Investigator considers the subject not suitable for the study.

4 SUBJECT INFORMATION AND INFORMED CONSENT

4.1 Preparation of the Information Sheet and Informed Consent Form

The principal investigator will author the written information and ICF(which are collectively referred to as "ICF"). The ICF will be a single document or set of documents and may be amended as necessary.

The document and its amendments will be submitted to MTPC and be approved by the institutional review board (IRB) before the study begins.

4.2 Contents of the Information Sheet

The written information must include at least the following items:

1) That the study involves research.
2) Study objectives
3) Name, title, and contact information of the investigator or subinvestigator
4) Study methods (including the study aspect of the clinical study, the inclusion criteria of subjects, and the probability for assignment to each treatment group)
5) Expected clinical benefits and risks or inconveniences.
6) Presence or absence of other treatments, and their important potential benefits and risks.
7) Expected duration of the subject's participation in the study.
8) That the subject's participation in the study is voluntary and that the subject may refuse to participate or discontinue from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
9) That the monitor, auditor, IRB, or regulatory authority should be granted access to the medical source documents, and the confidentiality of the subject should be secured at that time. And that by affixing subject's signature and seal or signing the consent form, the subject has authorized such access.
10) That if the results of the study are published, the confidentiality of the subject should be maintained.
11) The person(s) of the study site to contact for further information regarding the study and the right of subjects, and whom to refer or contact in the event of the study-related injury.
12) Compensation and treatment available to the subject in the event of the study-related injury.
13) The type of IRB to investigate and discuss whether it is appropriate or not to perform the clinical study, the items to be investigated and discussed by each IRB, and other items related to the study regarding the IRB.
14) Planned number of subjects involved in the study
15) The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study.

16) Conditions or reasons for the termination of participation in the study.

17) Anticipated expenses, if any, to the subject.

18) Anticipated payment, if any, to the subject (e.g., agreement for calculation of the amount of payment).

19) Items with which a subject should comply.

4.3 Methods for Obtaining Informed Consent

1) Before initiating the study, the (sub)investigator will provide the candidate subject with an explanation sheet/ICF that has been approved by the IRB and explain its contents thoroughly to the candidate subject. A clinical research coordinator may also provide a supplemental explanation. The (sub)investigator must provide the explanation based on the explanation sheet using as simple language as possible to make sure that the candidate subject understands, and must provide adequate responses to the candidate subject's questions. The (sub)investigator will confirm that the candidate subject has thoroughly understood the explanation before obtaining the candidate subject's written consent to participate voluntarily in the study.

2) Both the (sub)investigator who provided the explanation and the candidate subject will sign and date the ICF. If a clinical research coordinator provided a supplemental explanation, then this clinical research coordinator will also sign and date the ICF as well.

3) The (sub)investigator will, before the subject starts participating in the study, provide the signed and dated explanation sheet/ICF to the subject and store the original ICF properly, in accordance with the rules of the study site.

4) The date of informed consent acquisition and the version number of the ICF used for explanation will be recorded on the case report form.

4.4 Amendment of the Information Sheet and Informed Consent Form

1) Whenever important new information becomes available that may be relevant to the subject's consent, the (sub)investigator will promptly orally inform the subjects already participating in the study about this information, ascertain their willingness to continue participating in the study, and document this process in the medical records.

2) The principal investigator will promptly determine whether the ICF should be amended to reflect this information.

3) If determining that the ICF should be amended, the principal investigator must promptly amend the ICF and must again obtain the approval of the IRB.

4) The (sub)investigator will inform the subjects already participating in the study using the amended ICF approved by the IRB and obtain voluntary written consent from the subjects to continue participating in the study.

5) The informing (sub)investigator and the subject will sign and date the ICF as they did when

consent was first obtained. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also sign or affix the name and the seal to the document, and date it.

6) The (sub)investigator will give the signed and dated ICF to the subject and appropriately retained the original ICF according to study site procedures.

7) The date of informed re-consent acquisition and the version number of the ICF used for explanation will be recorded on the case report form (CRF).

5 STUDY DESIGN

5.1 Study Phase

Study phase: Phase I/II

5.2 Study Design

A randomized, multicenter, observer-blinded, placebo-controlled study with Japanese male and female subjects who are seronegative for SARS-COV-2 antibodies or negative for SARS-COV-2 antigen test at screening.

125 subjects will be randomized 4:1 and will receive the same 3.75 μg of MT-2766 or placebo. Subjects will receive two intramuscular (IM) injections 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once), of one of the following blinded treatments:

- Group 1: 3.75 μg of MT-2766 in a final volume of 0.5 mL (n=100)
- Group 2: Placebo for MT-2766 3.75 μg in a final volume of 0.5 mL (n=25)

In addition, subjects in Group 3 (n=20) will receive two IM injections of 1.875 μg MT-2766 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once) under open-label. The study may be completed even if fewer than 20 subjects in Group 3 are enrolled.

- Group 3: 1.875 μg of MT-2766 in a final volume of 0.25 mL (n=20)

Subjects will be screened up to 21 days in advance of the first vaccine administration and will demonstrate a satisfactory baseline medical assessment by history, general physical examination, hematological, biochemical, urinalysis and serological analysis. Although tests for SARS-CoV-2 antibodies and antigen will be performed at screening, negative subjects will be enrolled. On Day 0 and Day 21, vaccine administration will occur. Phone contacts will be made after each vaccine administration, specifically for review of the subject's safety and concomitant medication data. Visits to the study site will occur 3 days after each vaccine administration for key safety assessments, and 21 days after each vaccine administration for key safety and immunogenicity assessments.

Subjects will return to the study site on Day 128, Day 201, and Day 386 (3-month, 6-month, and 12-month safety follow-ups and immunogenicity assessments after the last vaccine administration).

In Group 1 and Group 2, the randomization code will be opened after data lock when all subjects in Groups 1 and 2 have reached Day 42. Once the study is unblinded, if the efficacy may be inadequate or unconfirmable, public vaccination will be recommended in Group 1 (3.75 μg of MT-2766). Once the study is unblinded, public vaccination will be recommended in Group 2 (placebo group). If subject receives the vaccination, the subject will be withdrawn from the study.

In Group 3, if Medicago determines that the efficacy may be inadequate or unconfirmable, all subjects in Group 3 will be recommended to receive public vaccination. If subject receives the vaccination, the subject will be withdrawn from the study.

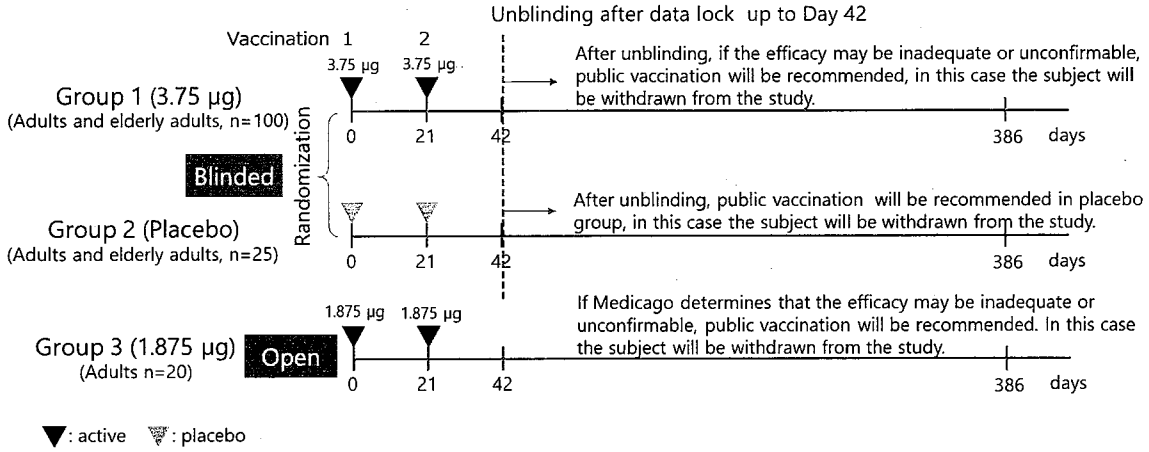

Figure 1 Study Flow

5.3 Rationale for Study Design and Treatment Regimens

5.3.1 Randomization

Group 1 (3.75 µg of MT-2766) and Group 2 (placebo) will be randomized. Age (< 65 and ≥ 65) will be used as stratification factors. On the other hand, Group 3 (1.875 µg of MT-2766) will be not randomized.

With regards to Group 1 and 2, randomization will be used to minimize bias in the assignment of subjects to two treatment groups, to increase the likelihood that known and unknown subject attributes (e.g. demographic and baseline characteristics) are evenly balanced across treatment groups and to enhance the validity of statistical comparisons across treatment groups within each Study Population. On the other hands, Group 3 will be not randomized because of its exploratory purpose.

5.3.2 Blinding

The study will be observer-blind to reduce potential bias during data collection and evaluation of the study endpoints. Group 1 (3.75 µg of MT-2766) and Group 2 (placebo) will be observer-blinded, on the other hand, Group 3 (1.875 µg of MT-2766) will be open-labeled.

Details of who will remain blinded during the study are presented in Section 5.4.2

5.3.3 Dose Selection and Treatment Regimens

In the study, a double dose levels of the MT-2766 (i.e. 3.75 µg or 1.875 µg CoVLP adjuvanted with AS03) will be tested in a two-dose regimen on Day 0 and Day 21.

The data from Phase 1 study (CP-PRO-CoVLP-019) in Canada clearly demonstrate the superiority of AS03 in the induction of anti-SARS-CoV-2 antibodies at all dose levels of CoVLP (3.75 µg, 7.5 µg and 15 µg,) compared to CoVLP alone. These data also suggest that

two doses of AS03-adjuvanted CoVLP are needed to achieve consistently high antibody responses in healthy adults since robust boosting in the Day 42 antibody response after two doses of AS03-adjuvanted CoVLP was observed at all dose levels, Medicago has decided to carry the lowest dose, 3.75 μg, forward into the Phase 2/3 study (CP-PRO-CoVLP-021). Medicago determined the dose for the current study to be 3.75 μg based on the dose selected for the Phase 2/3 study. In addition, Medicago would like to assess a dose of 1.875 μg, a half of 3.75 μg, because there were no apparent differences in the increase in neutralizing antibody titers at any dose level (3.75 μg, 7.5 μg and 15 μg) in the Phase 1 study. The dose of 1.875 μg provides half of the 1: 1 mixture of 3.75 μg of CoVLP and AS03 and therefore avoids the complexity of preparation of IMP. Half-dose AS03 has been tested in several influenza vaccine studies with satisfactory immune-boosting effects and slightly lower reactogenicity.

5.3.4 Route of Administration

The route of administration used for MT-2766 is the IM route, specifically in the deltoid muscle of the arm, since it reliable route of administration with good absorption compared to the subcutaneous route. The IM route was used in the Phase 1 and Phase 2/3 studies by Medicago.

5.4 Treatment Allocation and Blinding

5.4.1 Randomization

In the study, subjects in Group 1 and 2 will be randomized 4:1 to receive the 3.75 μg of MT-2766 and placebo. Eligible subjects will be randomized at the Day 0 visit using the interactive web response system (IWRS). Age (< 65 and ≥ 65) will be used as stratification factors.

No subjects will be randomized into the study more than once.

Subjects will be enrolled into treatment groups in the study based on a computer-generated randomization schedule prepared under the supervision of MTPC before the study. The details of treatment allocation will be specified in a separate procedure.

The treatment will be recorded along with a unique subject number for each subject.

5.4.2 Blinding

The study, Group 1 and Group 2, will be observer-blinded. Group 3 will be open label.

Until key code breaking of the study, the following individuals will not have access to treatment allocation (i.e. remain "blind"): the subjects, the Investigators and all personnel involved in the clinical conduct of the study (except the staff involved in the preparation and administration of the study vaccine), Sponsor, ICCC, and all personnel involved in sample analysis at the central and testing (Nab, ELISA, ELISpot, ICS [flow cytometry], serological, and virologic method SARS-CoV-2 diagnostics, etc.) laboratories.

Since the CoVLP formulation will have a different physical appearance and viscosity from the placebo, the site staff involved in the preparation and administration of the treatments will not be involved in any activity that could introduce a bias, such as the evaluations of reactogenicity

or AEs experienced by the subjects following vaccination.

5.5 Key Open

Key open will be performed after data lock up to Day 42 data in Group 1 and Group 2. If the efficacy may be inadequate or unconfirmable in Group 1 after key open, public vaccination will be recommended. After key open, public vaccination will be recommended in Group 2. If subject receives the vaccination, the subject will be withdrawn from the study prior to public vaccination.

5.6 Interim report

After unblinding, an interim report may be prepared with results of Group 1 and Group 2 only.

6 PLANNED NUMBER OF SUBJECTS AND STUDY PERIOD

6.1 Planned Number of Subjects

145 subjects will be enrolled.

Group 1: Subjects will receive 3.75 μg of MT-2766 in a final volume of 0.5 mL (n = 100).

Group 2: Subjects will receive placebo for MT-2766 3.75 μg in a final volume of 0.5 mL (n = 25).

Group 3: Subjects will receive 1.875 μg of MT-2766 in a final volume of 0.25 mL (n = 20).

The sample size is not based on power calculations but is set to meet the objectives of this clinical study.

For Group 3, the study may be completed even if fewer than 20 subjects are enrolled.

6.2 Study Period

The planned duration of the study is approximately 14 months, from screening procedures up to the end of the study.

7 INVESTIGATIONAL PRODUCT

7.1 Investigational Product

7.1.1 MT-2766

MT-2766 is the CoVLP vaccine composed of recombinant spike (S) glycoproteins expressed as VLPs with 1:1 (v:v) ratio of the adjuvant AS03 in a final volume of 0.25 mL (Group 3) or 0.5mL (Group 1).

For more information regarding the CoVLP formulation and AS03, refer to the current IB.

7.1.2 Placebo

The control product (placebo) will be composed of a phosphate-buffered saline solution (100 mM $NaKPO_4$, 150 mM NaCl) and 0.01 % polysorbate 80 at pH 7.4. The control product will be provided in vials.

Further specific information relating to the investigational product storage and shipment is provided in the Investigational Product Management Manual.

7.2 Study Vaccine Composition

The CoVLP vaccine is a sterile transparent to opalescent, colorless to yellowish liquid suspension. The CoVLP vaccine will be supplied in 3.1 mL multi dose vials. The S glycoprotein concentration in the vaccine will be 15 µg/mL for a final dosage of 3.75 µg in 0.25mL.

AS03 is an established effective adjuvant licensed for Arepanrix™ H1N1 and Arepanrix™ H5N1 (in Canada). The adjuvant is a whitish to yellowish homogeneous milky liquid emulsion and it will be provided in the original sterile vial container received from the manufacturer (GlaxoSmithKline). A 0.25 mL dose of AS03 represents one full human dose.

Further specific information relating to investigational product storage and shipment is provided in the Investigational Product Management Manual.

7.3 Investigational Product Packaging and Labeling

The CoVLP vaccine, AS03, and placebo will be packaged in separate boxes containing multiple vials of each investigational product.

The investigational product vials will have an English label as used in Medicago's Phase 2/3 study (CP-PRO-CoVLP-021). It is not possible to have a matching placebo in this study, therefore the vial labels will not be blinded. The study treatment will be prepared and administered by unblinded staff. Appropriate measures will be applied to maintain the observer-blindness of the blinded staff.

7.4 Preparation and Administration of Study Vaccine

The study treatments will be prepared by unblinded staff at the clinical site as described in the Preparation of Investigational Product Manual. The prepared study treatment will subsequently be administered to subjects by an unblinded staff. The unblinded staff must not be involved in the evaluation of any AEs or reactogenicity evaluations following vaccination.

The products to be used for study treatment administration will be handled in an aseptic manner.

The MT-2766 will be administered on study Day 0 and Day 21 as an IM injection of 0.5 mL (for subjects in Group1 and Group 2) or 0.25 mL (for subjects in Group3), into the deltoid muscle. For subjects, a 23 gauge needle of at least one inch or 2.5 cm in length can be used for vaccination.

The product administered will be recorded in study-specific documentation by the clinical site.

After drug accountability monitoring and reconciliation has been completed by the site and monitor, all study treatments (used and unused vials) will be returned to MTPC in accordance with instructions provided in the Investigational Product Management Manual.

Further specific information relating to investigational product storage, shipment and treatment preparation is provided in the Investigational Product Management Manual and Preparation of Investigational Product Manual.

7.5 Storage Conditions

The investigational products should be stored in an access-restricted area between 2 °C and 8 °C and protected from light; the vaccine should, however, be at room temperature before administration (i.e. the vaccine should not be administered cold and should be taken out of the refrigerator and brought to room temperature prior to administration).

The Investigational Product Management Manual provides additional details on storage of the investigational product.

7.6 Preparation, Handling, Storage, and Precautions for Use

After a clinical contract is concluded with the study site, MTPC will supply the investigational products. The investigational product manager will store and manage the investigational products in accordance with the Investigational Product Management Manual defined by MTPC.

The investigational product may not be used for any purpose not allowed in the protocol (e.g., other clinical studies, animal studies, basic research).

Further specific information relating to treatment preparation of investigational product is provided in the Preparation of Investigational Product Manual. The Investigational Product Management Manual provides additional details on handling and storage of the investigational product.

7.7 Drug Accountability

The head of the study site is responsible for ensuring that all study treatments received at the site are inventoried and accounted for throughout the study. The dispensing of study treatment to each subject must be documented on study-specific documentation.

The investigational products must be handled in strict accordance with the Investigational Product Management Manual and the vial label. The investigational products will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. The unblinded site staff will complete accountability for all investigational products (MT-2766 including CoVLP andAS03, and placebo). Refer to the Investigational Product Management Manual for details on the return of the used.

The study drug will be supplied only to subjects participating in the study. Returned study drugs may not be relabeled or reassigned for use for other subjects. The head of the study site agrees neither to dispense the study drug from, nor store it at, any site other than the study centers agreed upon with MTPC.

7.8 Procedures for Emergency Code Break

Any code break will be documented and reported to the MTPC in a timely manner by the Investigator. In a medical emergency, the Investigator may unblind the treatment for that subject without prior consultation with MTPC. The Investigator will open the emergency code in accordance with the "Procedure for Emergency Code Break" to identify the treatment group. In this procedure, the Investigator will disclose only the emergency code of the subject in question. In such an event, the Investigator will need to contact the Monitor as soon as possible after the unblinding to discuss the case. The treatment allocation should not be disclosed by the Investigator to the Monitor. In addition, the Investigator will prepare a document describing the reasons for the break and the range of CRFs that have been fixed before the break and submit it to MTPC.

MTPC will open the emergency code in accordance with the "Procedure for Emergency Code Break" to identify the treatment group. MTPC will record the reason for the break and the contents of deliberation and store them appropriately. MTPC will report the break to the Investigator and Medicago.

If a subject requests to participate in public vaccination before key open, the (sub)investigator must notify the emergency contact center in writing of the request and the subject identification code to be unblinded. The emergency contact center will unblind only the subject and identify the treatment group according to "Procedure for Emergency Code Break". The emergency contact center will notify the treatment group of the subject to the (sub)investigator. The (sub)investigator will inform the subject of the treatment allocation results. The emergency contact center will inform MTPC that the emergency key has been broken. Upon unblinding of a subject's treatment allocation, the subject will be withdrawn from the study and a withdrawal visit will be performed according to the withdrawal procedure (see Section 13.6).

8 STUDY METHODS FOR SUBJECTS

8.1 Subject Screening, and Preparation of the Enrolment Register and ID Code List

The Investigator will prepare a list of all the candidate subjects who have been screened (candidate subjects who have received informed consent) and will prepare a subject screening list. The Investigator will assign screening numbers to subjects who have consented to participate in the study, and will record in the subject screening list. In the list, key information to be used in the verification with source documents will be described.

The Investigator will also prepare a subject identification code list with the dates of informed consent, subject identification codes, etc. of the subjects who have been enrolled in the study (including subjects whose study treatments have been temporarily or permanently discontinued).

8.2 Subject Enrolment

The Investigator must confirm that the subject who has given consent to participate in the study meets the inclusion criteria and does not meet any of the exclusion criteria at the time of enrollment, enter necessary information in the IWRS, and inform the enrollment. After the registration, the Investigator will confirm the assessment results on the IWRS.

When the registration is completed, the Investigator and MTPC will receive the assessment result via E-mail from the IWRS. The Investigator, MTPC and Medicago cannot confirm the treatment. The unblind person (persons preparing investigational product) can confirm the treatment.

The investigational product manager will dispense the investigational product to the investigational product administration staff. The investigational product administration staff will vaccinate the subject. In this case, persons administering investigational product and preparing investigational product should take care not to identify investigational product to the subjects and other site staff (blinded staff).

The study collaborator can make the registration notificaltion on the IWRS as long as the approval of the Investigator is obtained and necessary information for the registration notification is recorded in the source documents by the Investigator.

8.3 Dose and Administration Method

The dose of MT-2766 has been selected based on the Phase 1 study data, including acceptable safety and immunogenicity profiles.

Subjects will receive two IM injections 21 days apart on Days 0 and 21, into the deltoid region of the alternating arm (each arm will be injected once), of one of the following:

- MT-2766 (Coronavirus-Like Particle COVID-19 vaccine with 1:1 (v:v) ratio of the adjuvant AS03);
- Placebo (phosphate-buffered saline solution and 0.01 % polysorbate 80 at pH 7.4).

Subjects in Group 1and Group 2 will receive the full standard dose of MT-2766 (3.75 μg) or

placebo in an injection volume of 0.5 mL. Subjects in Group 3 will receive MT-2766 (1.875 μg) in an injection volume of 0.25 mL.

8.4 Treatment Period

Two vaccinations separated by 21 days.

8.5 Prohibitions Prior to or During the Study Period

8.5.1 Prior and Concomitant Therapy

New or changed medications reported by the subject during the following periods will be recorded in the source documents as a concomitant medication as per the conditions outlined in the next paragraph. Since the new medication may be due to an AEs, the Investigator will explore the reasons for the change or for the new medication intake and document these AEs, if any.

Concomitant medications must be reported (reason for use, dates of administration, dosage, and route) if the use meets the following conditions:

- Within 30 days preceding vaccination: any treatments and/or medications specifically contraindicated (e.g. vaccines, any immunoglobulins or other blood products, or any immune modifying drugs, etc.);
- From randomization to Day 42, inclusive: any medication (including, but not limited to, over-the-counter medicines such as aspirin or antacids), vitamins, and mineral supplements;
- From Day 43 to the end of the study, inclusive: any concomitant medication(s) administered to treat an AESI, MAAE, SAE, or AE leading to withdrawal; any concomitant medication used to treat an AE that occurred before Day 42 and that is still being used afterwards (i.e. on-going use); COVID-19 vaccine administered after unblinding in Group 2 (with the cooperation of the subject);
- From the first vaccination and through to the end of the study, any concomitant medication used to treat conditions reported as medical history;
- From the first vaccination and through to the end of the study, any investigational medication or vaccine; any vaccine not foreseen in the study protocol (including immunization on an emergency basis).

8.6 Prohibited Therapy

The following medications or therapies are prohibited during the conduct of this study:

1. Administration of any vaccine (other than the study vaccine) up to Day 28 of the study as well as administration of any investigational or approved coronavirus vaccine (other than the study vaccine) up to end of the study. Immunization on an emergency basis during the study will be evaluated on case-by-case basis by the Investigator;

2. Use of any investigational or non-registered product during the study period. Subjects may not participate in any other investigational or marketed drug study while participating in this study until after the study;
3. Administration of any medication or treatment that may alter the vaccine immune responses, such as:
   - Systemic glucocorticoids;
   - Cytotoxic, antineoplastic, or immunosuppressant drugs;
   - Any immunoglobulin preparations or blood products, or blood transfusion.

   Administration of such medications should be specifically avoided up to Day 42 of the study. Use of any medication or treatment that may alter the vaccine immune responses due to a medical need during the study will be evaluated on case-by-case basis by the Investigator;
4. Use of prophylactic medications (e.g. antihistamines [H1 receptor antagonists], nonsteroidal anti-inflammatory drugs [NSAIDs], systemic and topical glucocorticoids, non-opioid and opioid analgesics) within 24 hours prior to administration of the second dose of the vaccine to prevent or pre-empt symptoms due to vaccination;
5. Use of prophylactic medications to prevent or pre-empt symptoms due to vaccination is specifically prohibited up to seven days after each vaccination (end of collection of solicited symptoms). A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an antipyretic is considered to be prophylactic when it is given in the absence of fever or any other symptoms, to prevent fever from occurring, vitamins used to boost immune system, etc.);
6. Use of any prescription antiviral drugs with the intention of COVID-19 prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have not been licensed for this indication, during the study.

If any of the Prohibited Therapy criteria are met by a subject, the subject may remain in the study however the inclusion of the subject's data within the immunogenicity per protocol (PP) set, immunogenicity Intent-to-treat (ITT) set, or Safety Analysis Set (SAS) may be impacted.

8.7 Subject Management

The (sub)investigator or the study coordinator will give daily life guidance to subjects with attention to the following points:

1) To receive inspection/examination on the designated days. To contact the (sub)investigator without fail and follow the instructions therefrom if the patient cannot visit the study site on the designated days;
2) To carry the study participation card and show it when the subject visit other hospitals or other departments. To make sure to inform the (sub)investigator or the study coordinator of the use of any drugs that are prescribed by a doctor other than those in charge of this study or drugs purchased at pharmacies. To make sure to inform the (sub)investigator or the study coordinator of the use of any new drugs that is started during the study, before

use.

3) Female subjects of childbearing potential must use an effective method of contraception after signing the ICF and agree to continue employing highly effective birth control measures for at least one month after the last study vaccination (or in the case of early termination, she must not plan to become pregnant for at least one month after her last study vaccination):

   The following relationship or methods of contraception are considered to be highly effective:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - Oral;
     - Intravaginal;
     - Transdermal;
   - Progestogen-only hormonal contraception associated with inhibition of ovulation:
     - Oral;
     - Injectable;
     - Implantable;
   - Intra-uterine device with or without hormonal release;
   - Credible self-reported history of heterosexual vaginal intercourse abstinence prior to and for at least one month after the last study vaccination. Abstinent subjects who are ovulating should be asked what method(s) they would use should their circumstances change, and subjects without a well-defined plan should be excluded;
   - Female partner.

4) To live carefully to prevent infection with COVID-19.

5) If a subject is suspected to have COVID -19 infection, the subject should be instructed as follows:

   - The subject will call study site (does not visit site)
   - The subject should contact the local government consultation desk where the subject lives, as instructed by the study site.
   - According to the instructions given by the consultation desk, have the subject visit the primary care physician or have the subject refer the subject to the nearest medical institution.
   - The subject will have PCR test.
   - The results will be communicated from the hospital or public health center where the test was performed.
   - If COVID-19 is positive, the public health center will inform the subject about medical treatment, specify the date of onset, ask about the course of subject's physical condition, and ask subject about subject's behavior. Hospitalization or a stay overnight in a

nursing home may be necessary.

- The subject will report the results of PCR test to the study site.

6) For subjects in Group 3, to refrain from participating in public vaccination programs until Day 42 because of the possibility of recommending the public vaccination after Day 42.

9 STUDY EVALUATIONS

9.1 Schedule for Tests and Observations

Table 1 shows the parameters of tests and observation, and the schedule.

Table 1 Time and Events Schedule

	Days −21 to Day −1 (screening)	Day 0		Day 1 (+1)	Day 3 (±1)	Day 8 (±1)	Day 15 (±1)	Day 21 (±2)[13]		Day 22 (±1)	Day 24 (±1)	Day 29 (±2)	Day 36 (±2)	Day 42 (±2)	Day49 (±2)
Visit Number	1	2		Phone[12]	3	Phone[12]	Phone[12]	4		Phone[12]	5	Phone[12]	Phone[12]	6	Phone[12]
		Before vaccination	After vaccination					Before vaccination	After vaccination						
Informed consent	X														
Demographics	X														
Medical history /Complications	X	X													
Prior medication	X	X													
Inclusion/Exclusion criteria	X	X													
Randomization (for Groups 1&2)		X													
Vaccine administration		X						X							
Physical examination	X	X	X		X			X	X		X			X	
Vital signs [1]	X	X	X		X			X	X		X			X	
Height(screening only)/Weight/BMI	X	X													
SARS-CoV-2 PCR test	X														
SARS-CoV-2 antibody test [2]	X														
Blood chemistry [3] /Hematology [4]	X	X			X			X			X			X	
Urinalysis[5]	X	X			X			X			X			X	
HIV/HBV/HCV	X														
Pregnancy test [6]	X[5]	X						X						X	
Immunogenicity -Serology (Nab assay/ ELISA/ anti-plant glycans IgE antibodies) [7]		X						X						X	
Immunogenicity - CMI response ((ELISpot and ICS) [8]		X						X						X	
Immediate surveillance			X						X						
Provide and collect paper diary and memory aid [9]			X		X			X			X			X	
Collection of solicited local/systemic AEs			X	X	X	X			X	X	X	X			
Concomitant medications [10]			←	—	—	—	—	—	—	—	—	—	—	—	→
AEs, SAEs, AESIs, MAAEs [11]			←	—	—	—	—	—	—	—	—	—	—	—	→
Collection of COVID-19 symptoms			Subjects will be instructed to contact the study site if they experience symptoms of COVID-19 from the day of the first vaccination (Day 0, post vaccination) until the end of the study.												

	Day 77 (±14)	Day 105 (±14)	Day 128[14] (±14)	Day 161 (±14)	Day 189 (±14)	Day 201 (±14)	Day 245 (±14)	Day 273 (±14)	Day 301 (±14)	Day 329 (±14)	Day 357 (±14)	Day 386 (±14)
Visit Number	**Phone[12]**	**Phone[12]**	**7**	**Phone[12]**	**Phone[12]**	**8**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**Phone[12]**	**9**
Informed consent												
Demographics												
Medical history /Complications												
Prior medication												
Inclusion/Exclusion criteria												
Randomization												
Vaccine administration												
Physical examination			X			X						X
Vital signs[1]			X			X						X
Height(screening only)/Weight/BMI												
SARS-CoV-2 PCR test												
SARS-CoV-2 antibody test[2]						X						X
Blood chemistry[3] /Hematology[4]												
Urinalysis[5]												
HIV/HBV/HCV												
Pregnancy test[6]			X									
Immunogenicity -Serology (Nab assay/ ELISA/ anti-plant glycans IgE antibodies)[7]			X			X						X
Immunogenicity - CMI Response ((ELISpot and ICS)[8]						X						X
Immediate surveillance												
Provide and collect paper diary and memory aid[9]			X			X						X
Collection of solicited local/systemic AEs												
Concomitant medications[10]	←											→
AEs, SAEs, AESIs, MAAEs[11]	←											→
Collection of COVID-19 symptoms	Subjects will be instructed to contact the study site if they experience symptoms of COVID-19 from the day of the first vaccination (Day 0, post vaccination) until the end of the study.											

1) Resting blood pressure (BP), pulse rate (PR), respiratory rate (RR), and body temperature.
2) Anti-N antibodies will be measured at screening, Days 201 and 386.
3) Biochemistry (serum): Sodium, Potassium, Urea, Creatinine, Glucose, Bilirubin (total), Albumin, Total protein, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma glutamyltransferase (GGT), Cholesterol (total, HDL, LDL), Triglycerides, Chloride, Calcium, Phosphorus.
4) Hematology: Hemoglobin, Hematocrit, Red blood cells, Platelets, Mean platelet volume (MPV), Neutrophils, Mean cell hemoglobin (MCH), Mean corpuscular hemoglobin

concentration (MCHC), Mean cell volume (MCV), White cell count (total, WBC), Lymphocytes, Monocytes, Eosinophils, Basophils

5) Urinalysis: Macroscopic examination (color, clarity), pH, Specific gravity, Glucose, Protein, Occult blood
6) It will be tested in serum at screening and in urine at Days 0, 21, 42, and 128.
7) On Days 21 and 128, the immunogenicity- serology blood sample will be collected for the Nab assay and ELISA only. Anti-plant glycan IgE antibodies will only be measured on Days 0, 42, 201 and 386.
8) Blood samples may not be collected for all subjects.
9) If subject cannot use electronic diary, paper diary and memory aid will be acceptable.
10) From Day 43, concomitant medication collection will be limited to those used to treat an SAE, medically attended adverse event (MAAE), AE leading to withdrawal, AEs of special interest (AESIs), or an AE that occurred before Day 42 and that is still being used afterwards (i.e. on-going use).
11) AEs will be collected up to Day 49; SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be collected through to the end of the study.
12) The study site should contact the subject via the electronic diary, phone, fax or email.
13) All efforts will be done to have subjects returning on planned date for Day 21 activities. If for any reason the visit is done before or after this planned date, subsequent visits/procedures will be adjusted accordingly.
14) Any subject who withdraws the study will be asked to undergo Day 128 visit procedures within two weeks of withdrawal, if the subject agrees. If a subject is withdrawn from Day 1 to Day 29, solicited local/systemic AEs are including. If a subject is withdrawn from Day 1 to Day 49, unsolicited AEs are investigated. If deemed necessary by (sub)investigator, necessary tests such as biochemistry, hematology, or urinalysis will be performed.

9.2 General COVID-19 Precautions at Study Sites

Sites participating in this study will have processes in place locally for following recommendations of the local Public Health authorities for the management of COVID-19. Subjects will be asked to follow good hygiene and safe physical distancing measures such as wearing a face mask on site, frequent hand hygiene, and maintaining a physical distance of 2 meters (or 6 feet) from others, except during procedures where staff must come into close proximity of subjects (e.g. vaccination, blood draws, collecting vital sign measurements).

Staff at the clinical sites will also follow the same good hygiene and safe physical distancing measures as the subjects at the site. In addition, the staff will be responsible for disinfecting materials and/or areas between each use by subjects and staff. All staff involved with on-site procedures will have a back-up member who is qualified to perform the same duties / responsibilities in the event that a member of the staff is infected with SARS-CoV-2 or comes into contact with an individual known to have COVID-19 and is restricted to self-isolation and following the recommendations of the local Public Health authorities for the management of COVID-19.

9.3 Study Procedures

9.3.1 Subject informed consent

Prior to performing any study procedures, the subjects will be allocated to randomized observer-blinded groups (Group 1and Group 2) or open-labeled group (Group 3) by the Investigator, and the Investigator (or designated personnel) will fully inform the subject of the nature and scope of the study, potential risks and benefits of participation, and the study procedures involved and will answer all questions prior to requesting the subject's signature on the ICF. The subject's consent must be obtained prior to performing any study-related procedures; the consent process must be clearly recorded and the signed ICF retained in the source documents. A copy of the ICF must be provided to the subject.

9.3.2 Screening (Visit 1)

Screening assessments will be performed from Day -21 to Day -1. The following procedures will be performed at the initial screening visit (Visit 1) for the study:

- Review the signature of the ICF;
- Review the inclusion and exclusion criteria and determine and record the subject's eligibility to participate in this study. The eligibility must be confirmed by the Investigator after review of all procedures and findings and prior to randomization;
- Review and record demographics (gender, date of birth, age, race, and ethnicity) and body measurements (BMI, weight [kg], and height [cm]) data. BMI is to be calculated as body weight (kg) divided by the square of height (m); the BMI result will be rounded to one decimal place using the standard convention. For the measurement of body weight, subjects will be lightly clothed, without shoes;
- Review and record medical history, including the grade of any medical conditions

(medical conditions are to be graded using the same scale as for AEs; see Section 12.1.2). The medical history should record significant problems active at the time of screening and present within the preceding six months. Problems that have been clinically inactive for more than six months preceding screening, but which might alter the subject's current or future medical management, should also be noted (e.g. cancer, autoimmune disease, known mitral valve prolapse or a remote history of a seizure disorder);

- Review and record co-morbid conditions. The comorbidities include but are not limited to obesity (moderate or greater), hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular diseases, chronic kidney diseases, or be immunocompromised persons (e.g., organ transplant recipients, or patients receiving cancer chemotherapy).
- Review and record current and previous medication use (up to 30 days prior to study vaccine administration), with the following exception (refer to exclusion criterion no. 4):
  - For subjects who have been administered the following medication or treatment, review and record current and previous medication use up to the time period specified for the medication or treatment:
    - Cytotoxic, antineoplastic, or immunosuppressant drugs – within 36 months prior to vaccination;
    - Any immunoglobulin preparations or blood products, blood transfusions – within 6 months prior to vaccination;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Perform a vital signs measurement, including resting blood pressure (BP), pulse rate (PR), respiratory rate (RR), and infra-axillary body temperature. Infra-axillary body temperature will be collected in degrees Celsius using a digital thermometer. The BP will be taken after the subject has been in a seated position as per the site's standard procedure. The BP should be taken by cuff (manual or automated are both acceptable). BP, HR, and RR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents. Inclusion of subjects with an out-of range BP or PR or RR measurement will be based on the Investigator's judgement;
- Collet sample for SARS-CoV-2 PCR test;
- Collect screening blood samples for biochemistry, haematology, and serology (HIV, Hepatitis B, and Hepatitis C screening) for analysis as well as to test for SARS-CoV-2 antibodies. Sample blood collection at the screening visit should be performed under fasting conditions (approximately 12 hours) for cholesterol and triglyceride analysis;
- Perform urinalysis;
- Perform serum pregnancy testing for female subjects of childbearing potential at screening;

Rescreening will be acceptable without re-consent within 30 days from obtaining the first consent. The (sub)investigator will record the reason for rescreening in the source documents.

9.3.3 Day 0 Dose 1 Vaccination (Visit 2)

Emergency equipment must be available on site and appropriate treatment must be instituted as soon as possible in the event of anaphylaxis or any other immediate hypersensitivity reaction. The (sub)investigator will be on-site on vaccine administration days and for the duration of the observation period (minimum of 30 minutes after vaccination) for the last subject dosed on that day. The Investigator will be available on call for the remainder of the study. A physician should be immediately available at the clinical site to administer treatment or to apply procedures for any immediate AEs/SAEs.

Subjects withdrawn before vaccination may be replaced at the discretion of the Investigator. Replacement subjects will receive the treatments intended for the withdrawn subject.

9.3.3.1 Pre-vaccination

The following procedures will be performed on Day 0 (Visit 2) prior to vaccination.

- Record changes in medical history and medications and confirm that the subject continues to meet all inclusion and no exclusion criteria;
- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature (OT). OT will be collected in degrees Celsius using a digital thermometer. The BP will be taken after the subject has been in a seated position as per the site's standard procedure. The BP should be taken by cuff (manual or automated are both acceptable). BP, PR, and RR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents. Inclusion of subjects with an out-of range BP or PR or RR measurement will be based on the Investigator's judgement;
- Measure the BMI; for this visit, only weight will be measured while the height will be obtained from that measured at the initial screening visit. The BMI result will be rounded to one decimal place using the standard convention. For the measurement of body weight, subjects will be lightly clothed, without shoes;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Collect urine sample for urinalysis;
- Collect blood samples for biochemistry and haematology;
- Collect a urine sample for female subjects of childbearing potential and perform a urine dipstick (or similar) pregnancy test. No study vaccine must be administered to a childbearing potential female until a negative result is obtained and documented;
- If the subject is judged eligible for the study and is still willing to participate in the study, for Group 1 and Group 2, randomize the subject into the study;
- After confirmation of eligibility and randomization, collect baseline blood samples to test for immunogenicity (serology [Nab assay, ELISA and anti-plant glycans IgE antibodies] and CMI) assessments (for CMI, blood samples may not be collected for all subjects); prepare and store these samples until shipment to the central laboratory.

9.3.3.2 Vaccination

Once all pre-vaccination procedures have been completed and subject eligibility determined, the subject will be randomized (if applicable) and the study vaccine will be administered IM into the deltoid muscle of the non-dominant (if possible) arm, as described in the Preparation of Investigational Product Manual. In order to prevent possible confounding of vaccination site reactions, whenever possible, blood samples will not be collected from the same arm as the one used for vaccination. The arms used, both for blood collection and vaccination, will be documented in the source documents. For subjects, a 23 gauge needle of at least one inch or 2.5 cm in length can be used for vaccination. The preparation and administration of the study vaccine will be performed by an unblinded site staff.

9.3.3.3 Thirty Minutes Post-vaccination

The post-vaccination observations will be performed by a site staff. The following safety observation procedures will be performed for all subjects immediately following study vaccine administration:

- Subjects will remain in the clinic for at least 30 minutes post-vaccination for observation. The observation period will include an assessment of immediate solicited local and systemic AEs. Solicited local and systemic AEs occurring within 30 minutes post-vaccination will be recorded in the diary and corresponding electronic case report form (eCRF). All unsolicited AEs occurring within 30 minutes post-vaccination will be recorded in the subject source and AE eCRF. Any unusual signs or symptoms reported during the initial 30 minutes post-vaccination will result in continued close monitoring. Based on their condition, subjects may be asked to remain in the clinic for their safety for more than 30 minutes after vaccination (the reason will be recorded in the source documents). All data (including the assessment of solicited local and systemic AEs) will be recorded in the source documents during and after the observation period. Refer to Section 11.1 for details regarding the assessment of AEs and/or solicited local and systemic AEs;
- During the observation period, subjects will be provided with a measurement device template for measuring (in mm) solicited local AEs of erythema (redness) and swelling and a digital thermometer for recording daily temperature (in degrees Celsius). Subjects will also be provided with a diary and will be shown how to enter their data in the diary. Each subject will be provided with the following instructions on the measurements they are to make:
  - How to collect his/her oral temperature in degrees Celsius with the provided digital thermometer:
    - From the evening of Day 0 to the evening of Day 7, oral temperature will be measured at approximately the same time each evening and the results recorded in the diary;
    - The subject is to also take his/her oral temperature if he/she feels feverish and to record the highest temperature of the day. In the event that a temperature ≥ 38.0 °C is obtained, the subject will be allowed to take over-the-counter antipyretics (e.g. acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) and will be advised to increase the frequency of oral temperature measurements to approximately

every four hours, until he/she is no longer febrile (fever is defined as a temperature of ≥ 38.0 °C). The subject is to document medication intake, which will be reviewed by the site personnel;

- How to measure any solicited local AEs, including erythema (redness) and swelling diameter at the injection site using the measurement template supplied for this purpose; subjects will also be requested to evaluate pain at the injection site. Local AEs will be assessed every day starting in the evening of Day 0 and up to the evening of Day 7 and the results will be recorded. The severity of solicited local AEs will be graded according to the Food and Drug Administration (FDA) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007], as presented in Table 3.
- How to grade, on a daily basis from the evening of Day 0 through to the evening of Day 7, each of the solicited systemic AEs and their severity (as per the same guidance used for solicited local AEs; see Table 3) [FDA 2007] and to record the worst grade of the day for each of these solicited systemic AE. The instructions will include how to examine and grade swelling in the neck and axilla and to record any unusual feeling and/or swelling;
- Instruct the subjects to perform measurements of local and systemic AEs at approximately the same time each day from Day 0 to Day 7 (preferably in the evening);
- Subjects will be advised that they will be asked about the occurrence of any symptoms or events requiring medical attention and the use of any concomitant medication during the 21-day post-vaccination period, after each vaccination, and until the end of the study. Subjects will also be provided with a memory aid to record unsolicited AEs and any concomitant medication use and will be shown how to enter their data in the memory aid;
- Subjects will be instructed to contact the clinical site for any unsolicited AEs and/or solicited local and systemic AEs of greater than Grade 2 (moderate). Based on their condition, the Investigator may request that the subject return to the clinic for evaluation;
- Subjects will be advised on emergency contact information and instructions for contacting study personnel. Subjects will be advised to immediately contact the Investigator (or his/her designee) in the event of an SAE or a medical emergency. Subjects will be provided with a phone contact number and be instructed to call if any suspected reaction to the vaccination is felt to be significant or of concern;
- Subjects will be advised to notify their health care professional(s) (e.g. primary care physician) that they are participating in a clinical research study of a SARS-CoV-2 / COVID-19 vaccine (See Section 12.2);
- Advise each subject to report to the clinical site if he/she has tested positive for COVID-19;

- After the 30-minute observation period (allowed window of +30 minutes) is completed, measure vital signs (BP, PR, RR, and oral temperature) as described in Section 11.1.5 and perform a symptom-directed physical examination. Any out-of-range measurements will be assessed by the Investigator (or his/her designee) and any further action will be determined upon his/her medical decision;

- Provide appointments (date and time) for the next planned visit to the clinical site (Day 3) and for the Days 1, 8 and 15 phone, electronic diary, fax or email contacts;
- The subject will be released from the clinical site once all relevant Day 0 post-vaccination procedures have been completed and the subject is in stable condition.

9.3.4 Day 1, Day 8 and Day 15 (Telephone Contact)

The post-vaccination phone contacts will be performed by blinded site staff. The following procedures will be performed during the phone contact (acceptable interval of + 1 day for Day 1, and ± 1 day for Day 8, and ± 1 day for Day 15):

The phone contact is including via electronic diary, fax and email.

- Investigate any unsolicited AEs and/or solicited local and systemic AEs and any use of concomitant medications. If necessary, the Investigator may request that the subject return to the clinic for evaluation.
- For any unsolicited AEs and/or solicited local and systemic AEs of greater than Grade 2 (moderate), the Investigator should be informed within 24 hours of the time the clinical site is made aware of the event. The Investigator may request that the subject return to the clinic for evaluation;

In the event that a subject cannot be reached via phone, electronic diary, fax or email, at least three attempts within allowed time window should be made in order to reach the subject.

9.3.5 Day 3 Follow-up (Visit 3)

The post-vaccination follow-up visit procedures will be performed by site staff at the clinical site. The following procedures will be performed during the Day 3 visit (± 1 day):

- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Collect urine sample for urinalysis;
- Collect blood samples for biochemistry and haematology;
- Review the diary and memory aid content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs, SAEs, AESIs, or MAAEs) are recorded appropriately;
- Advise the subjects to immediately contact the Investigator or his/her designee, in the event of any AE that requires a visit to an emergency room and/or hospitalization;
- Remind each subject to immediately report to the clinical site any symptoms associated with COVID-19 or if he/she has tested positive for COVID-19. Ensure that subjects have the memory aid listing the COVID-19 symptoms and contact information for the study site;

- Remind the subjects of their next telephone contact (date and time).

9.3.6 Day 21 Dose 2 Vaccination (Visit 4)

If for any reason the Day 21 visit is done before or after the planned date, then subsequent visits/procedures will be adjusted accordingly.

9.3.6.1 Pre-Dose 2 Vaccination

The pre-vaccination procedures will be performed by site staff. The following procedures will be performed during the Day 21 (± 2 days) visit prior to vaccination for the study:

- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Collect urine sample for urinalysis;
- Collect blood samples for biochemistry and haematology;
- Collect blood samples for immunogenicity (serology [Nab assay and ELISA] and CMI) assessments (for CMI, blood samples may not be collected for all subjects); prepare and store these samples until shipment to the central laboratories;
- Perform urine (dipstick or similar) pregnancy testing for female subjects of childbearing potential. No study vaccine must be administered to a childbearing potential female until a negative result is obtained and documented;
- Review the memory aid content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated in the paper memory aid;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs, SAEs, or AESIs) are recorded appropriately;
- Advise the subjects to immediately contact the Investigator or his/her designee, in the event of any AE that requires a visit to an emergency room and/or hospitalization;
- Assess the subject for contraindications to the second vaccination according to Section 13.3;
- The IWRS will assign the same treatment assignment at Day 21 as Day 0.

9.3.6.2 Dose 2 Vaccination

The same procedures will be performed during the administration of the vaccine on Day 21 as will be performed during the administration of the vaccine on Day 0 (see Section 9.3.3.2 for detailed procedures), with the following exception regarding which arm to use for IM administration:

- The study vaccine should be administered IM into the deltoid muscle of the alternate arm

if possible (i.e. the arm not used for the previous dose administration). Record the administration, left or right arm, in the subject source documents.

9.3.6.3 Post-Dose 2 Vaccination

The same procedures will be performed following the administration of the vaccine on Day 21 as will be performed following the administration of the vaccine on Day 0 (see Section 9.3.3.3 for detailed procedures), with the following exceptions:

- Provide appointments (date and time) for the next planned visit to the clinical site (Day 24) and for Days 22, 29 and 36 telephone contacts;
- The subject will be released from the clinical site once all post-vaccination procedures have been completed and the subject is in stable condition.

9.3.7 Day 22, Day 29 and Day 36 (Telephone Contact)

The same procedures will be performed during the phone contacts on Day 22, Day 29 and Day 36 as were performed during phone contacts on Day 1, Day 8 and Day 15 (acceptable interval of ± 1 day for Day 22, and ± 2 days for Day 29 and Day 36, see Section 9.3.4 for detailed procedures).

9.3.8 Day 24 (Visit 5)

The same procedure will be performed during the Day 24 visit as were performed during the follow-up visit on Day 3 (see Section 9.3.5 for detail procedures).

9.3.9 Day 42 (Visit 6)

The same procedure will be performed during the Day 42 visit as were performed during the pre-vaccination portion of the visit on Day 21 (see Section 9.3.6.1 for detail procedures), with the following exceptions:

- Collect blood samples to test for immunogenicity (serology [Nab assay, ELISA and anti-plant glycans IgE antibodies] and CMI) assessments (for CMI, blood samples may not be collected for all subjects); prepare and store these samples until shipment to the central laboratory.
- Review the memory aid content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated in the paper memory aid. Collect the paper memory aid and provide subjects with another memory aid for the collection of safety data from Day 43 to Day 201 if necessary;
- Remind each subject to immediately report to the clinical site any symptoms associated with COVID-19 or if he/she has tested positive for COVID-19. Ensure that subjects have the memory aid listing the COVID-19 symptoms and contact information for the study site;

- Provide appointments (date and time) for the next telephone contacts and the next planned visit to the clinical site (Day 128).

9.3.10 Day 49 (Telephone Contact)

The same procedures will be performed during the phone contacts on Day 49 as were performed during phone contacts on Day 1, Day 8 and Day 15 (acceptable interval of ± 2 days, see Section 9.3.4 for detailed procedures). After key code breaking, the post-vaccination phone contacts will be not limited to blinded site staff.

9.3.11 Monthly Calls Thereafter (Telephone Contact)

Subjects should be contacted by telephone once every month (every 28 days ± 14 days; the second vaccination visit date as starting reference or last day of contact with the clinic site or Investigator if a second vaccination did not occur) by blinded staff (by blinded or unblinded staff after unblinding). The following procedures will be performed during the phone contacts:

The phone contact is including via electronic diary, fax and email.

- Investigate any AEs and any use of concomitant medications. The Investigator may request that the subject return to the clinic for evaluation.

In the event that a subject cannot be reached via phone, electronic diary, fax or email, at least three attempts within allowed time window should be made in order to reach the subject.

9.3.12 Day 128 (Visit 7)

The post-vaccination visit procedures will be performed by site staff at the clinical site. The following procedures will be performed during the Day 128 visit (± 14 days):

- Review the memory aid content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated in the paper memory aid. If necessary, collect the paper memory aid and provide subjects with another memory aid for the collection of safety data;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs ongoing from Day 49, SAEs, AESIs, or MAAEs) are recorded appropriately;
- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Perform urine (dipstick or similar) pregnancy testing for female subjects of childbearing potential.
- Collect blood samples for immunogenicity (serology [Nab assay and ELISA]) assessments; prepare and store these samples until shipment to the central laboratories;
- Remind each subject to immediately report to the clinical site any symptoms associated

with COVID-19 or if he/she has tested positive for COVID-19. Ensure that subjects have the memory aid listing the COVID-19 symptoms and contact information for the study site;

- Provide appointments (date and time) for the next telephone contacts and the next planned visit to the clinical site (Day 201).

Any subject who withdraws the study will be asked to undergo Day 128 visit procedures within two weeks of withdrawal, if the subject agrees. If a subject is withdrawn from Day 1 to Day 29, solicited local/systemic AEs are investigated. If a subject is withdrawn from Day 1 to Day 49, unsolicited AEs are investigated. If deemed necessary by (sub)investigator, necessary tests such as biochemistry, hematology, or urinalysis will be performed.

9.3.13 Day 201 (Visit 8)

The post-vaccination visit procedures will be performed by site staff at the clinical site. The following procedures will be performed during the Day 201 visit (± 14 days):

- Review the memory aid content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated in the paper memory aid. If necessary, collect the paper memory aid and provide subjects with another memory aid for the collection of safety data;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs ongoing from Day 49, SAEs, AESIs, or MAAEs) are recorded appropriately;
- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Collect blood sample to test for SARS-CoV-2 antibodies;
- Collect blood samples for immunogenicity (serology [Nab assay and ELISA], CMI and anti-plant glycans IgE antibodies) assessments (for CMI, blood samples may not be collected for all subjects); prepare and store these samples until shipment to the central laboratories;
- Remind each subject to immediately report to the clinical site any symptoms associated with COVID-19 or if he/she has tested positive for COVID-19. Ensure that subjects have the memory aid listing the COVID-19 symptoms and contact information for the study site;
- Provide appointments (date and time) for the next telephone contacts and the next planned visit to the clinical site (Day 386).

9.3.14 Final Visit – Day 386 (Visit 9)

The post-vaccination final visit procedures will be performed by site staff at the clinical site. The following procedures will be performed during the Day 386 visit (± 14 days):

- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs ongoing from Day 49, SAEs, AESIs, or

MAAEs) are recorded appropriately. Collect the paper memory aid;

- Confirm that the subject has continued to comply with protocol requirements (e.g. no use of prohibited concomitant medications, reporting of any COVID-19 symptoms);
- Perform a vital signs measurement, including resting BP, PR, RR, and oral temperature;
- Perform a history- or symptom-directed physical examination. The physical examination will be performed by the Investigator or sub-Investigator;
- Collect blood sample to test for SARS-CoV-2 antibodies;
- Collect blood samples for immunogenicity (serology [Nab assay, ELISA and anti-plant glycans IgE antibodies] and CMI) assessments (for CMI, blood samples may not be collected for all subjects); prepare and store these samples until shipment to the central laboratories.

9.3.15 Surveillance for COVID-19 Cases

The surveillance will be performed until the end of the study:

- Subjects will be instructed to contact the study site in case they suspect infection of COVID-19;
- If a subject reports any symptom(s) of COVID-19:
  - Collect information regarding COVID-19 as AEs:
  - Collect information on any associated concomitant medication use;
- Ensure subjects have the memory aid listing the symptoms of COVID-19 and contact information for the study site; ensure subjects use the diary or memory aid, as applicable, to record reportable information.

In the event that a subject cannot be reached via telephone, he/she may be contacted by fax, text message or via email (if these contacts are available). However, the telephone should be the initial and preferred means of communication. At least three attempts within allowed time window should be made in order to reach the subject.

10 COLLECTION OF BLOOD SAMPLES

All subjects will have blood sampled. Subjects will have blood volumes drawn of up to approximately 335 mL over a period of 386 days (Table 2).

Table 2 Estimated Blood Volume Drawn

Type of Sample	Volume per Sample (mL)									
	Visit 1 (Day -21 to -1)	Visit 2 (Day 0)	Visit 3 (Day 3)	Visit 4 (Day 21)	Visit 5 (Day 24)	Visit 6 (Day 42)	Visit 7 (Day 128)	Visit 8 (Day 201)	Visit 9 (Day 386)	Total Volume of Blood per Subject (mL)
Serology (HIV, hepatitis B, C or SARS-CoV-2 antibodies)	11							3*	3*	17
Biochemistry, haematology, pregnancy test	10	8	8	8	8	8				50
Serology for immunogenicity (Nab assay, ELISA)		10		10		10	10	10	10	60
CMI response (PBMC)**		40		40		40		40	40	200
Total volume of blood per subject (mL)	21	58	8	58	8	58	10	53	53	327

*: Only SARS-CoV-2 antibodies are tested
**: Blood samples may not be collected for all subjects.

11 ASSESSMENT METHODS

11.1 Safety Evaluations

Safety and tolerability will be evaluated by solicited local and systemic adverse events (immediate solicited adverse events within 30 minutes post-vaccination and solicited adverse events up to seven days after each vaccination), unsolicited AEs within 30 minutes post-vaccination and up to 28 days after the second vaccination (Day 49), SAEs, AESIs, MAAEs, and AEs leading to withdrawal up to the end of the study. In addition, events will be monitored for possible VAED, hypersensitivity components, and potential immune-mediated diseases, from all reported events during the study (collected AEs, SAEs, AESIs, MAAEs, and AEs leading to withdrawal). Clinical safety methods will include repeated urine, blood chemistry, and haematology testing.

11.1.1 Solicited Local and Systemic Adverse Events

Subjects will be monitored for both solicited local AEs (erythema, swelling, induration and pain at the injection site) and solicited systemic AEs (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck) from the time of each vaccination through seven days. While the subjects remain in the clinic following vaccine administration (at least 30 minutes), staff will monitor them for solicited local and systemic AEs; after release from the clinic facility, from the evening of each vaccination to the evening of the seventh day after each vaccination, the subject will measure and record the subject's local and systemic AEs in the diary.

The intensity of the solicited local and systemic AEs will be assessed by the subject, documented in the diary, and graded as: mild (1), moderate (2), severe (3) or potentially life threatening (4) (please refer to Table 3). The causal relationship of all solicited local and systemic AEs will be considered related.

The Investigator should assess solicited AEs and determine if any meet the criteria for SAE. Any solicited local or systemic AEs that meet the criteria for SAE should be reported to MTPC within 24 hours (Section 12.1.6) and entered as an SAE in the eCRF.

Table 3 Severity Grades for Solicited Local and Systemic Adverse Events

Symptoms	Severity				
	None	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Injection Site Adverse Events (Solicited Local Adverse Events)					
Erythema (redness)	< 25 mm	25 – 50 mm	51 – 100 mm	> 100 mm	Necrosis or exfoliative dermatitis
Swelling	< 25 mm	25 – 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis

Symptoms	Severity				
	None	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Induration	< 25 mm	25 – 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Solicited Systemic Adverse Events					
Fever (°C)	< 38.0 °C	38.0 – 38.4 °C	38.5 – 38.9 °C	39.0 – 40.0 °C	> 40.0 °C
Headache	None	No interference with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Muscle aches	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Joint aches, chills, feeling of general discomfort or uneasiness (malaise), swelling in the axilla, swelling in the neck	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Results in a visit to emergency room (ER) or hospitalization

11.1.2 Unsolicited Adverse Events

All spontaneous unsolicited AEs occurring up to Day 49 will be reported in the "Adverse Event" screen in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related. Thereafter, from Day 50 to the end of the study, SAEs, AEs leading to withdrawal, MAAEs and AESIs will be monitored and reported in the eCRF.

The intensity of unsolicited AEs will be graded as: mild (1), moderate (2), severe (3) or potentially life threatening (4), according to the FDA Guidance for Industry [FDA 2007]. Their causal relationship with the study vaccine will be assessed by the Investigator (definitely not related, probably not related, possibly related, probably related or definitely related); see Section 12.1.9 for a definition of these causal relationships.

11.1.3 SARS-CoV-2 Positive Reports

Confirmed COVID-19 cases will be recorded as AEs. Also, confirmed COVID-19 cases will be reported according to the process for reporting SAEs, in the event such case may meet the definition of an SAE. Any potential COVID-19 case that is not a confirmed event and does meet the criteria for an SAE will be reported. The Investigator must report the SAE to MTPC within 24 hours (see Section 12.1.6) of becoming or being made aware.

Following the first vaccination, each subject will be asked to report symptoms associated with COVID-19 during the study. COVID-19 will be defined as the presence of a laboratory-confirmed (virologic method) SARS-CoV-2 infection with the occurrence of a new onset of one or more of the following symptoms:

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

11.1.4 Clinical Laboratory Tests

Blood samples for biochemistry and hematology, HIV, Hepatitis B and Hepatitis C markers in serum and urine samples for urinalysis will be collected according to the Time and Events Schedule (see Table 1). Blood samples for testing for SARS-CoV-2 antibodies will be also collected according to the Time and Events Schedules (see Table 1). In addition, serum or urine samples from all females of childbearing potential for pregnancy testing will be collected. Any laboratory result outside of the testing laboratory's normal range will be classified as 'clinically significant' or 'not clinically significant' by the site Investigator, with appropriate documentation. Any laboratory test performed at Screening with a value outside the normal range may be repeated (prior to vaccination) at the discretion of the Investigator. Repeated tests will be considered the Baseline results.

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the source documents. The tests to be performed by the laboratory are presented in Table 4.

Table 4 Clinical Laboratory Tests for the Study

Biochemistry (serum):	
Sodium	Alkaline phosphatase
Potassium	Alaninetransferase (ALT)
Urea	Aspartatetransferase (AST)
Creatinine	Gamma glutamyltransferase (GGT)
Glucose	Cholesterol (total, HDL, LDL)
Bilirubin (total)	Triglyceride
Albumin	Chloride
Total protein	Calcium
	Phosphorus
Haematology:	
Haemoglobin	Mean cell haemoglobin (MCH)
Hematocrit	Mean cell concentration (MCHC)
Red blood cells	Mean cell volume (MCV)
Platelets	Lymphocytes
Mean platelet volume (MPV)	Monocytes
White cell count (total, WBC)	Eosinophils
Neutrophils	Basophils
Serology:	
HIV	Hepatitis B
Hepatitis C	
Urinalysis:	
Macroscopic examination (color, aspect)	Glucose
pH	Protein
Specific gravity	Blood

Other clinical laboratory tests include tests to measure SARS-CoV-2 antibodies at screening, Days 201 and 386, and SARS-CoV-2 PCR at screening for all subjects, and a serum pregnancy test at screening and a urine (dipstick or similar) pregnancy test prior to randomization on Day 0 and on Days 21, 42 and 128 for all female subjects of childbearing potential.

All protocol required safety laboratory parameters are defined in study-specific documentation.

11.1.5 Vital Signs

Vital signs measurements (resting BP, PR, RR, and oral temperature) will be performed as part of screening procedures, prior to vaccination (on Day 0 and Day 21), and after the post-vaccination 30-minute surveillance period (and repeated if deemed necessary by the Investigator). In addition, vital signs measurements will be performed at the clinic site visits on Day 3, Day 24, Day 42, Day 128, Day 201, and Day 386.

Oral temperature will be collected in degrees Celsius using a digital thermometer provided by MTPC. The OT measurement should not be collected immediately following consumption of a hot or cold beverage or after smoking.

BP will be taken after the subject has been in a seated position as per the site's standard procedure. BP should be taken by cuff (manual or automated are both acceptable). BP, PR and RR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents.

11.1.6 Physical Examinations

A history- or symptom-directed physical examination will be performed as part of screening procedures, prior to vaccination (on Day 0 and Day 21), and after the post-vaccination 30-minute surveillance period by the (sub)Investigator. In addition, history- or symptom-directed physical examinations will be performed at the clinic site visits on Day 3, Day 24, Day 42, Day 128, Day 201, and Day 386 by (sub)Investigator.

11.1.7 Pregnancy

Female subjects who become pregnant during the study will be followed for safety. The Investigator, or his/her designee, will collect pregnancy information on any subject who becomes pregnant or is pregnant while participating in this study. The Investigator will record pregnancy information on the Pregnancy Report Form (see Appendix 2) and submit it to MTPC (see Section 12.1.6) within 24 hours of learning of a subject's pregnancy post-first vaccination. The subject will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to MTPC, if available. Generally, follow-up will be no longer than eight weeks following the estimated delivery date.

While pregnancy itself and elective termination of a pregnancy for non-medical reasons are not considered to be an AE/SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded in the Pregnancy Report Form or as an SAE and will be followed. A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the Investigator, will be reported to MTPC. While the Investigator is not obligated to actively seek this information from former study subjects, he/she may learn of a pregnancy through spontaneous reporting.

11.2 Immunogenicity Evaluations

Immunogenicity will be evaluated by the humoral immune response (serology) and the CMI response induced in subjects on Days 0, 21, 42, 128 (serology only), 201, and 386 in all subjects.

For CMI response, blood samples may not be collected for all subjects.

The blood samples for immunogenicity will be analyzed in one or more central laboratories; information on processing and the central laboratories will be provided in the study-specific documentation.

11.2.1 Immunogenicity Endpoints

See Section 2.2.1, 2.2.2 and 2.2.3.

Point estimates and 95 %CI will be calculated for all immunogenicity endpoints and responses

for the treatment groups will be compared using descriptive statistics.

12 ASSURANCE OF SUBJECT SAFETY

12.1 Definitions

12.1.1 Serious Adverse Events

An SAE is any untoward medical occurrence (whether or not considered to be related to the study vaccine) that, at any dose:

- Results in death;
- Is life-threatening (at the time of the event);

Note: the term "life-threatening" in the definition of an SAE refers to an event that put the subject at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe;

- Requires inpatient hospitalization (≥ 24 hours) or prolongation of existing hospitalization (elective hospitalizations/procedures for pre-existing conditions that have not worsened are excluded);
- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect;
- Is another medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject's health or may require an intervention to prevent one of the other outcomes listed in the definition above. These events should be considered serious. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse. See Section 12.1.6 for initial SAE reporting by the Investigator.

12.1.2 Adverse Events

An AE or adverse experience is defined as any untoward medical occurrence in a subject or clinical investigation subject who was administered a pharmaceutical product, with or without a causal relationship with the treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to a medicinal product.

Information such as the date and time of onset and resolution (duration), intensity (defined below), seriousness, any required treatment or action taken, outcome, relationship to the investigational vaccine, and whether the AE caused withdrawal from the study will be collected.

The intensity of all AEs will be graded as mild (1), moderate (2) severe (3), or potentially life threatening (4), according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007] for the events covered in the guidance and the following definitions for all other events:

Mild (Grade 1):	The AE is easily tolerated and does not interfere with usual activity;
Moderate (Grade 2):	The AE interferes with daily activity, but the subject is still able to function;
Severe (Grade 3):	The AE is incapacitating and the subject is unable to work or complete usual activity;
Potentially life-threatening (Grade 4):	The AE is likely to be life-threatening if not treated in a timely manner.

Note: According to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007]: *"Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis. These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers."* and *"Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values."*

The Investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the investigational product or not) until the outcome of the AE has been determined.

If any of the solicited local or systemic AEs persist beyond Day 7 after each vaccination (when applicable), these will also be recorded as unsolicited AEs. In this case, the AE start will be set as eight days post-vaccination. The subject will be requested to note when the AE resolves and to report this information to the Investigator or site staff at the next visit at the clinical site or contact.

The clinical importance of AEs will be determined based upon the Investigator's judgment. The Investigator must ensure that any sample obtained to follow-up on an AE is properly labeled and stored. The Investigator and site staff should institute any supplementary investigations of significant AEs based on the clinical assessment of the likely causative factor. This may include seeking the opinion of a specialist in the field of the AE.

All unsolicited AEs occurring up to Day 49 must be reported in the "Adverse Event" screen in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related. Thereafter, from Day 50 through to Day 386, SAEs, MAAEs, AEs leading to withdrawal, and AESIs will be monitored and reported in the eCRF. Additional details on eCRF entries can be found in the eCRF completion guidelines.

12.1.3 Medically Attended Adverse Events

Medically attended adverse events are defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

12.1.4 Adverse Events of Special Interest

12.1.4.1 Adverse Events of Special Interest for the Coronavirus-Like Particle COVID-19 Vaccine

12.1.4.1.1 Vaccine-associated Enhanced Disease

Safety signal of VAED after exposure to MT-2766 will be closely monitored and assessed by retrieving data for this AESI as follows: AEs within the system organ class (SOC): immune system disorders and high level group term (HLGT): lower respiratory tract disorders (excluding obstruction and infection), cardiac disorders, signs and symptoms not elsewhere classified, vascular disorders, heart failures, arteriosclerosis, stenosis, vascular insufficiency and necrosis, cardiac arrhythmias, myocardial disorders, and vascular hemorrhagic disorders. High level term (HLT): renal failure and impairment and preferred term (PT): pericarditis, coagulopathy, deep vein thrombosis, pulmonary embolism, cerebrovascular accidents, peripheral ischemia, liver injury, Guillain-Barre syndrome, anosmia, ageusia, encephalitis, chilblains, vasculitis, erythema multiforme (based on standardized Medical Dictionary for Regulatory Activities (MedDRA®) classification) [Law 2020, Law 2020a] that require inpatient hospitalization (≥ 24 hours) and have laboratory confirmed SARS-CoV-2 infection will be monitored for assessment of any potential case of VAED. As this list can be updated during the study, any further changes to the AESI terms will be updated in the AESI list.

12.1.4.1.2 Hypersensitivity Reactions

All reported events will also be monitored for hypersensitivity reactions after exposure to the CoVLP formulation. Severe allergic reactions are considered to be an important potential risk (based on the theoretical risk that using plants for the production of biotherapeutics may induce hypersensitivity), Medicago will require that supervision are available to manage any possible anaphylactic reactions in this study. To collect data on these events, Medicago will closely monitor and assess allergic reactions assessed as related to the investigational product as AESIs.

12.1.4.2 Adverse Events of Special Interest for the Adjuvants

12.1.4.2.1 Potential Immune-Mediated Diseases and Other AESI

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. Adverse events that need to be recorded and reported as pIMDs include those listed in Appendix 3.

However, the Investigator will exercise their medical and scientific judgement in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in Appendix 3, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been

eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to Investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the Investigator must complete, date and sign an Serious Adverse Events Report.

12.1.5 Expectedness of an Adverse Drug Reaction

An "unexpected" adverse reaction is one in which the nature or severity of the event is not consistent with information in the current version of the IB. Expedited reporting to the regulatory authorities is required if an SAE occurs that is both unexpected and considered possibly, probably, or definitely related to the study vaccine.

12.1.6 Initial SAE, AESI, and Pregnancy Reports Reporting by the Investigator

Details on safety reporting are defined in study-specific documentation, including SAE processing, country-specific reporting requirements, regulatory unblinding, roles and responsibilities of different stake holders, and contact details of personnel responsible for safety reporting. A brief summary of salient information is presented below.

All post-vaccination SAEs, AESIs, and pregnancy reports will be reported from the time of receiving the study vaccine on Day 0 through to the end of the study (final scheduled visit). The Investigator (or designee) must report all SAEs, AESIs, and pregnancy reports whether considered related to the study vaccine or not to MTPC within 24 hours of the Investigator learning of the event (Appendix 1 and Appendix 2). The Investigator must also complete, sign, and date the paper SAE report form and/or pregnancy report form and send, via e-mail or Fax, a copy to MTPC within 24 hours of awareness of event.

Serious AEs will be reported to the IRB by the Investigator according to the IRB's policy and procedures.

12.1.7 Follow-up Reporting by the Investigator

All AEs, SAEs and AESIs regardless of causality, will be followed as described in Section 12.1.2. When appropriate, documentation of any medical tests or examinations performed will be provided to document resolution/stabilization of the event.

12.1.8 Reporting of SAEs Occurring after Study Termination

All SAEs occurring during the study period will be followed until resolution or for a period of 30 days from the final subject's visit (whichever occurs first), regardless of conclusion of the study. However, all related SAEs occurring during the study period will be followed until resolution or stabilization.

A post-study AE/SAE is defined as any event that occurs after Day 386. Active follow-up for

AEs or SAEs will continue until Day 386 for all subjects. However, after Day 386, if the Investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the investigational product, the Investigator will promptly notify MTPC for Reporting SAEs. These related SAEs will be followed until resolution or stabilization.

12.1.9 Causal Relationship

The Investigator must make the determination of relationship to the study vaccine for each unsolicited AE. The causal relationship of all solicited local and systemic AEs will be considered related. The Investigator should decide whether, in his/her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational vaccine. If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational vaccine and the occurrence of the AE, then the AE should be considered "definitely related", "probably related", or "possibly related". Otherwise, if no valid reason exists for suggesting a possible relationship, then the AE should be classified as "probably not related" or "definitely not related". The following guidance should be followed:

Definitely Not Related:	The AE is clearly not related to the administration of the study vaccine. Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study vaccine administration; and/or a causal relationship is considered biologically implausible.
Probably Not Related:	There is no medical evidence to suggest that the AE is related to the study vaccine. The event can be readily explained by the subject's underlying medical condition or concomitant therapy or lacks a plausible temporal relationship to the study vaccine.
Possibly Related:	A direct cause and effect relationship between the study vaccine and the AE has not been demonstrated but there is a reasonable possibility that the event was caused by the study vaccine.
Probably Related:	There probably is a direct cause and effect relationship between the AE and the study vaccine. A plausible biologic mechanism and temporal relationship exist and there is no more likely explanation.
Definitely Related:	There is a direct cause and effect relationship between the AE and the study vaccine.

AE outcomes will be classified as recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, or death.

12.1.10 Reporting of SAEs to Health Authorities and IRB

Medicago will be responsible for reporting SAEs that are deemed both possibly related to the study vaccine and considered to be unexpected ('unexpected' refers to events that do not appear

in the package labeling or in the study vaccine IB) to the regulatory authorities in an expedited manner.

The Investigator will be responsible for reporting the SAEs that meet IRB reporting requirements directly to the relevant ethical review board as soon as possible, and will also provide the ethical review board with any safety reports prepared by Medicago or its designee.

All SAEs that are suspected, unexpected serious adverse reactions (SUSARs) should be reported to regulatory authorities by electronic transmission as soon as possible but, in no event, later than seven calendar days for deaths and life-threatening events, and 15 calendar days for other SAEs after Medicago's or MTPC's initial receipt of the information. These events should be followed to resolution, stabilization, or return to baseline, regardless of conclusion of the study.

12.1.11 Stopping Rules

The study may be paused if any of the following events occur:

- Any subject experiences an SAE after administration of the vaccine that is considered related to vaccine;
- If 5 or more subjects experience the same or similar AE:
  - Experience the same or similar Grade 3 or higher solicited local AE or systemic AE, within 7 days after administration of the vaccine;
  - Experience the same or similar Grade 3 AE or higher unsolicited AE (including symptoms, signs or laboratory safety AEs) that is judged anything but unrelated to the vaccine;

If any of the stopping rules are met, Medicago will decide whether to continue the study and record the reason.

12.2 Notification to the Subject's Primary Care Physician

The (sub)investigator will ascertain whether a subject is seeing doctors other than those of this study during the study period. When a subject is seeing other doctors, the (sub)investigator will inform those doctors of the participation of the subject in the study upon consent of the subject. The (sub)investigator or a study coordinator will provide a study participation card to subjects for notifying other doctors via the subject of subject participation in the study and instruct the subjects to present the card on receiving care at another hospital or in another department.

13 SUBJECT WITHDRAWAL CRITERIA AND PROCEDURES

13.1 Temporary Contraindications

An exclusion criterion that renders subjects ineligible for the study may be temporary in nature:

- Acute disease defined as presence of any moderate or severe acute illness with or without a fever within 48 hours prior to vaccination.

If a subject is considered ineligible due to this "temporary contraindication", the subject should be considered as a screening failure. Following the resolution of such conditions, a subject may be rescreened under a new screening number and, if considered eligible by the Investigator, be enrolled in the study.

13.2 Screening Failures

Screening failures are subjects who have signed the study-specific ICF but are not eligible for enrollment (subjects who were not randomized), due to failure on one or more of the inclusion or exclusion criteria or because the subject withdrew consent prior to randomization.

Recording of screening failures documented in the study records maintained at the participating clinical sites. Screen failures will not receive a safety follow-up. Any subjects who are considered as a screening failure should be indicated as such. A screening failure subject can be rescreened. The subject who is rescreened will be re-reviewed the eligibility and enrolled if eligible.

13.3 Contraindications for Subsequent Vaccination

The following events constitute absolute contraindication to the further administration of the study treatments at Day 21; if any of these events occur during the study, the subject will not receive an additional dose of vaccine but will continue with the Day 128 scheduled visit (see Section 9.3.12), the Day 201 scheduled visit (see Section 9.3.13), the Day 386 scheduled visit (see Section 9.3.14) and all telephone contact visits at the discretion of the Investigator:

- Pregnancy (see Section 11.1.7);
- Clinically-apparent hypersensitivity of any grade that is considered by the site Investigator to be related to the investigational product in response to first vaccine administration;
- Have a laboratory-confirmed SARS-CoV-2 infection;
- Acute disease within 48 hours prior to vaccination (acute disease is defined as presence of any moderate or severe acute illness with or without a fever);
- Diagnosis of pIMD;
- Experience a possibly related, probably related, or definitely related SAE or Grade 3 or higher related AE that cannot be clearly attributed to another cause;
- Discovery of any health condition which, in the Investigator's opinion, may place the subject at increased risk from receipt of further vaccination; or discovery of a change in the subject's status which may render him/her unable to comply with protocol-mandated safety

follow-up. If an AE occurred prior to or at the time of the Day 21 scheduled visit, the subject may be discontinued at the discretion of the Investigator or the subject may be vaccinated at a later date, however, within the time window specified in the protocol (see Section 9.3.6.1). The subject must be followed until resolution of the event as with any AE (see Section 12.1.2).

13.4 Subject Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time without prejudice to their future medical care by the physician or the study site. Subjects who withdraw or are withdrawn from the study after vaccination will not be replaced.

Every reasonable effort will be made to ensure that each subject complies with the protocol and completes all study visits. However, a subject may withdraw or be withdrawn from participation in study if:

- The subject withdraws consent;
- The subject is lost to follow-up;
- The subject is incarcerated or incapacitated during the conduct of the clinical study;
- The subject has moved away from the study area and can no longer fulfill the terms of their participation in the clinical study;
- The subject displays non-compliance to the terms of their participation in the clinical study (based on Investigator's opinion);
- The Investigator has lost confidence in the subject's ability to adhere to the terms of their participation in the clinical study (based on Investigator's opinion);
- Safety reasons as judged by the Investigator;
- Medicago or the regulatory authority(ies) terminates the clinical study.

Once the study is unblinded, if the efficacy may be inadequate or unconfirmable in Group 1, public vaccination will be recommended in Group 1. Once the study is unblinded, public vaccination will be recommended in Group 2. In Group 3, if Medicago determines that the efficacy may be inadequate or unconfirmable, all subjects in Group 3 will be recommended to receive public vaccination. If subject receives the vaccination, the subject will be withdrawn from the study. The withdrawal procedures (Section 13.6) should be performed before vaccination whenever possible.

13.5 Follow-up of Discontinuation of Subsequent Vaccination

All subjects who receive a study vaccine will be followed for safety until the end of the study, if permitted by the subject.

A subject may be considered discontinued from treatment if the subject does not receive both vaccine administrations (i.e. second vaccine administration is not completed; see Section 13.3 for details). A subject discontinuation from the treatment may not necessarily be discontinued from the study as further study procedures and follow-up may be performed (safety and

immunogenicity), if permitted by the subject.

13.6 Withdrawal Procedure

Withdrawal subjects will be those who leave the study before Day 386, for whatever reason; withdrawal subjects will not be replaced. Any subject who withdraws the study will be asked to undergo Day 128 visit procedures within two weeks of withdrawal, if the subject agrees. If a subject is withdrawn from Day 1 to Day 29, solicited local/systemic AEs are investigated. If a subject is withdrawn from Day 1 to Day 49, unsolicited AEs are investigated. If deemed necessary by (sub)investigator, necessary tests such as biochemistry, hematology, or urinalysis will be performed.

All withdrawal subjects must be reported to MTPC. The reason for withdrawal should be documented in the subjects' records and in the appropriate section of the eCRF. The eCRF must be completed up to and including the time of the drop-out/final assessment.

The (sub)Investigator or clinical research coordinator will record the date of discontinuation, reason for discontinuation, etc. in the case report form. Furthermore, if the study is discontinued because of an adverse event, the (sub)Investigator or study coordinator will record the term of the event that resulted in discontinuation in the case report form. The date of discontinuation will be the date on which the (sub)Investigator made the decision to discontinue the study and informed the subject that the subject was being discontinued from the study; however, if the (sub)investigator is not able to get ahold of the subject, then the date of discontinuation will be the date on which the decision was made to discontinue the subject from the study.

13.7 Lost to Follow-up Procedures

Every attempt will be made to contact study subjects who are lost to follow-up. At least three contacts will be attempted and recorded in the source documents. As a last resort, one registered letter requesting contact with the site will be sent to any subject with whom the site staff no longer has contact. All attempts at contact will be documented in the subject's source documents and entered in the eCRF.

14 STATISTICAL ANALYSIS

14.1 Determination of Sample Size

The sample size is not based on a formal statistical power calculation but was considered to be adequate to meet the objectives of the study.

14.2 Analysis Set

The statistical analysis will be based on separate analysis sets, defined as follows:

Safety Analysis Set (SAS):	All subjects who received at least one dose of either the MT-2766 or placebo.
Immunogenicity Intent-to-treat (ITT) Set	All subjects who receive at least one dose of either the MT-2766 or placebo and who have at least 1 post-baseline Immunogenicity assessment.
Immunogenicity Per Protocol (PP) Set	Immunogenicity ITT set who do not have any major protocol violations, and who received either the MT-2766 or placebo. For the Day 21 analysis, this should include the subjects who received the first vaccine dose and had Day 0 and Day 21 immunogenicity sample collections. For the Day 42 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 42 immunogenicity sample collections. For the Day 128 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 128 immunogenicity sample collections. For the Day 201 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 201 immunogenicity sample collections. For the Day 386 analysis, this should include the subjects who received both vaccine doses and had Day 0 and Day 386 immunogenicity sample collections.

All safety analyses will be performed using the SAS. The analyses of all immunogenicity endpoints will be performed using the Immunogenicity PP set as the primary analysis population, and the immunogenicity ITT set, as a secondary analysis population.

14.3 Data Handling

Unless otherwise specified, the baseline values will be the last non missing value before receiving the first dose of the MT-2766 or placebo.

Procedures for the handling of any missing, unused or spurious data will be described in the statistical analysis plan (SAP).

14.4 Statistical Analysis Plan

A general description of the statistical methods used to analyze the safety and immunogenicity data is outlined below. Complete details will be provided in the SAP, which will be finalized prior to database lock.

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System® (SAS®) software (version 9.4 or higher).

Unless otherwise stated in the SAP, continuous data will be summarized descriptively: N (number of subjects), n (number of observations), mean, standard deviation (SD), minimum, median and maximum. Categorical data will be summarized using frequency tables (frequency and percent).

All individual subject data will be listed, where applicable.

14.4.1 Analysis of Demography and Other Baseline Subject Characteristics

Demographic and other baseline information will be summarized for each analysis set depending the type of data (continuous, categorical).

14.4.2 Analysis of Primary Endpoints

The following primary immunogenicity and safety endpoints are for Group 1 and Group 2.

Safety:

Immediate AEs (30 minutes after each vaccination) and solicited local and systemic AEs reported up to seven days after each vaccination will be summarized by treatment using descriptive statistics. In addition, all unsolicited AEs, SAEs, AEs leading to subject withdrawal, AESIs, MAAEs, and deaths reported up to 21 days after each vaccination will be summarized by treatment using descriptive statistics.

Immunogenicity:

- GMT (Day 0, Day 21, and Day 42): The point estimates and the corresponding two-sided 95 % CI by treatment group will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 0, Day 21, and Day 42): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group will be calculated and reported; The SC rate is defined as the proportion of subjects achieving SC in the analysis set:

- For subjects with detectable Nab titer at Day 0 (i.e. baseline Nab titer ≥10): a ≥ 4-fold increase in Nab titers between Day 0 and Day 21 and Day 42, respectively;
- For subjects with undetectable Nab titer at Day 0 (i.e. baseline Nab titer < 10): Nab titer of ≥ 40 on Day 21 and Day 42, respectively;

- GMFR: the geometric mean of the ratio of GMTs (Day 21/Day 0 and Day 42/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 21 and Day 0 and between Day 42 and Day 0, with treatment group as main effect and baseline titer as covariate.

GMT will be compared between treatment groups using the analysis of variance (ANOVA) model. GMFR will be compared using the ANCOVA model on the log-transformed titer. For SC rate, Fisher's exact tests will be used to compare between the treatment groups.

The specific Th1 CMI response induced on Day 0, Day 21, and Day 42 will be measured by the number of T cells secreting IFN-γ, using ELISpot, for each treatment group. The specific Th2 CMI response induced on Day 0, Day 21, and Day 42 will be measured by the number of T cells secreting IL-4, using ELISpot, for each treatment group. The response will be compared between treatment groups and timepoints using appropriate non-parametric (Wilcoxon) models.

Additional details will be provided in the SAP.

14.4.3 Analysis of Secondary Endpoints

The following secondary immunogenicity and safety endpoints are for Group 1 and Group 2.

Safety:

SAEs, AEs leading to subject withdrawal, AESIs, MAAEs, and deaths reported from Day 43 to Day 201 and from Day 202 to Day 386 will be summarized by treatment using descriptive statistics.

Subjects with normal and abnormal urine, hematological, and biochemical test results within three days of first (Day 0) and second (Day 21) injections will be summarized using frequency tables.

Immunogenicity:

- GMT (Days 128, 201, and 386): The point estimates and the corresponding two-sided 95 % CI by treatment group will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Days 128, 201, and 386): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 128/Day 0, Day 201/Day 0, and Day 386/Day 0).

For the analyses of the total IgG antibody response, the GMT and SC rate will be calculated on Day 0, Day 21, Day 42, Day 128, Day 201, and Day 386 as well as the GMFR (Day 21/Day 0, Day 42/Day 0, Day 128/Day 0, Day 201/Day 0, and Day 386/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 21 and Day 0, between Day 42 and Day 0, Day 128 and Day 0, Day 201 and Day 0, and Day 386 and Day 0 with treatment group as main effect and baseline titer as covariate.

The specific Th1 CMI response induced on Day 201 and Day 386 will be measured by the number of T cells secreting IFN-γ, using ELISpot, for each treatment group. The specific Th2 CMI response induced on Day 201 and Day 386 will be measured by the number of T cells secreting IL-4, using ELISpot, for each treatment group. The responses will be compared between treatment groups and timepoints using appropriate non-parametric (Wilcoxon) models. Additional details will be provided in the SAP.

14.4.4 Analysis of Exploratory Endpoints

Immunogenicity:

For Group 1 and Group 2, the CMI response induced on Day 0, Day 21, Day 42, Day 201, and Day 386 will be measured by the percentage of CD4+ T cells expressing functional markers, using flow cytometry (ICS), for each treatment group. The responses will be compared between treatment groups and timepoints using appropriate non-parametric (Wilcoxon) models. Additional details will be provided in the SAP.

For Group 1 and Group 2, the specific antibody response against plant glycans induced on Day 0, Day 42, Day 201 and Day 386, will be analyzed by evaluating the percentage of subjects with detectable IgE levels at each timepoint for each treatment group and the percentage of subjects with IgE levels, relative to baseline (Day 0), that are greater than the limit of detection at Day 42, Day 201, and Day 386 for each treatment group. Additional details will be provided in the SAP.

For Group 3, the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed.

Safety:

For Group 3, the same analyses as the primary and secondary endpoints in Groups 1 and Group 2 will be performed.

14.4.5 Analysis of Immunogenicity Endpoints

For Group 1 and Group 2, the Nab/IgG ratio will be calculated as the antilog of the Nab/IgG ratio and 95 % CI of log transformed titer values. The ratio will be compared between treatment groups using ANOVA.

14.4.6 Analyses of Safety Endpoints

14.4.6.1 Adverse Events

The original terms used in the eCRFs by Investigators to identify AEs will be coded using the

MedDRA®. All eCRF reported AEs with onset post-vaccination will be included in the safety analyses. All unsolicited AEs occurring on vaccination, within 21 days after each vaccination and up to Day 49 and SAE will be classified by system organ class (SOC) and preferred term (PT).

Overall summary will be conducted through primary and secondary safety endpoints.

Frequency count and the number of unique subjects with an AE will be tabulated by treatment.

14.4.6.2 Clinical Laboratory Tests

Clinical laboratory test results (hematology and chemistry) and their changes from baseline will be summarized by visit using descriptive statistics.

14.4.6.3 Vital Signs

Vital sign results and their changes from baseline will be summarized by visit using descriptive statistics.

14.4.6.4 Physical Examinations

Physical examination data will be listed by subject.

14.5 Amendments to the Statistical Analysis Plan

If the SAP described in this section is going to be amended before the data lock, the amendment and the reason for the amendment will be described in the SAP and the clinical study report. If the analysis method is going to be changed or an additional analysis performed after the data lock, the amendment and the reason will be described in the clinical study report, and the results will be distinguished from the results of the analysis that had been planned.

15 PROTOCOL COMPLIANCE, DEVIATIONS, AND CHANGES

15.1 Agreement on the Protocol and Compliance with the Protocol

Before reaching an agreement with MTPC about the protocol, the Investigator must consult with MTPC and thoroughly consider whether conducting the study is ethically and scientifically justified using the protocol, the latest version of the IB, and other necessary data provided by MTPC and Medicago.

Based on the findings, the Investigator will agree with MTPC about the contents of the protocol and sign or affix the name and the seal to a written agreement, and date it with thein order to certify protocol compliance.

15.2 Protocol Deviations and Changes

The (sub)investigator must not deviate from or change the protocol without prior agreement with MTPC documented in writing and written approval based on prior review by the IRB. The (sub)investigator may deviate from or change the protocol without the prior written agreement of MTPC and prior approval of the IRB in a medically unavoidable situation such as to avoid exposing a subject to acute risk.

In such situations, the Investigator must as quickly as possible notify MTPC, the head of study site, and IRB of the deviation or change along with the reason and, when appropriate, proposed protocol amendments. The Investigator will then receive approval, the acknowledgment of the head of study site, and written agreement from MTPC.

The (sub)investigator must document all protocol deviations. The Investigator will create a written record of the reason for any noncompliance with the protocol to avoid exposing a subject to acute risk or for another medically necessary reason and immediately submit this record to MTPC and the head of the study site, retaining a copy thereof.

The Investigator will promptly submit a written report to MTPC, the head of study site, and IRB about any study changes with a significant impact on the conduct of the study or that could expose the subjects to greater risk.

16 AMENDMENT OF THE PROTOCOL

MTPC will amend the protocol while the study is ongoing when it is considered necessary to make changes to the protocol. MTPC will discuss and agree on the content of amendment with the Investigator, immediately inform the head of the study site in writing, and obtain approval from the IRB through the head of the study site.

If the head of the study site instructs modifications on the basis of the opinions of the IRB, MTPC will judge whether the changes are appropriate and amend the protocol if necessary. MTPC will discuss and agree on the content of amendment with the Investigator, immediately inform the head of the study site in writing, and obtain approval from the IRB through the head of the study site.

If modifications are considered necessary on the basis of discussion with the Investigator, MTPC will judge whether the changes are appropriate and amend the protocol if necessary. MTPC will agree on the content of amendment with the Investigator, immediately inform the head of the study site in writing, and obtain approval from the IRB through the head of the study site.

17 STUDY DISCONTINUATION AND TEMPORARY SUSPENSION

17.1 Criteria for Termination or Suspension of the Study

MTPC will consider whether it is appropriate to continue the study in the entire study sites or in some of the study sites;

1) Important information related to the quality, efficacy, or safety of the investigational product is learned that impacts the justification of the study;
2) A protocol changes with which a study site cannot comply is required;
3) The head of the study site, based on the opinion of the IRB, requests a protocol revision that is unacceptable to Medicago;
4) The head of study site indicates that the study should be terminated in accordance with a decision by the IRB.
5) The study site is in major or continual violation of good clinical practice (GCP), the protocol, or the study contract.

17.2 Termination or Suspension of the Entire Study by the Sponsor

If Medicago decides to terminate or suspend the entire study, MTPC will immediately inform the head of the study site and the regulatory authority in writing and provide the reasons for this decision. When the head of the study site is notified by MTPC of termination or suspension of the study, the head of the study site immediately informs the details of the fact and the reasons therefor to the investigator and the IRB in writing.

When the Investigator is notified by MTPC, via the head of the study site, of termination or suspension of the study, the investigator will immediately inform the subjects and guarantee appropriate treatment.

When the study is terminated, the subjects will be treated in accordance with Section 13.6

17.3 Termination or Suspension of the Study at a Study Site by the Investigator or the IRB

If the Investigator terminates or suspends the study by his/her own discretion, the Investigator will immediately inform the details of the fact and the reasons therefor to the head of the study site in writing. The head of the study site will immediately inform MTPC and the IRB in writing.

When the IRB decides to terminate or suspend the study on the basis of its own judgment, the IRB will immediately inform the details of the fact and the reasons therefor to the head of the study site in writing. The head of the study site will immediately inform the investigator and MTPC in writing.

17.4 Termination of the Study due to Cancellation of Contract with Study Sites

If MTPC terminates the study for the reason that the study site has committed significant or

continuous violations of GCP, this protocol, or the clinical study contract during the study period, MTPC will immediately inform to the regulatory authority.

18 MATTERS CONCERNING CASE REPORT FORMS

18.1 Format of Case Report Forms

In this study, eCRF utilizing an electronic data capture (EDC) system will be used. The Investigator will check the eCRF, and the electronically signed eCRF will be considered the original. Solicited AEs will be reported via electric or paper diary. The laboratory test facilities will report the results of the laboratory tests to MTPC in electronic format but will not record the results in the eCRF. The results of immunogenicity measurement will be recorded in the report of the institution for immunogenicity measurement, but not in the case report form.

18.2 Definitions of Data Directly Entered in the Case Report Forms, and Identification of Data to Be Classified as Source Data

If the data on eCRF are going to be considered source data, then this will be specified separately in writing before the start of the study by MTPC and the Investigator.

18.3 Instructions for Completing Case Report Forms

The (sub)Investigator or a clinical research coordinator will complete the case report forms according to the instructions below. The case report forms will be prepared in accordance with the eCRF Entry Manual which will be provided separately by MTPC.

1) Before entries are made in the case report forms, MTPC will engage in user control by assigning a user ID and password to the (sub)Investigators and study coordinators. The (sub)Investigators and study coordinators will keep and not share their assigned user ID and password. Data will be entered by (sub)Investigators and study coordinators granted entry privileges.
2) Case report forms will be prepared for subjects who have been administrated the investigational product.
3) The Investigator may make entries in all case report form fields. The sub investigators may make entries in all case report form fields other than the electronic signature field. The study coordinators may transcribe information from the medical records and otherwise transcribe information from the source documents when no medical decision is required.
4) A reason for each change or revision to case report form entries will be provided as electronic information.
5) The Investigator will electronically sign each case report form in the EDC system after confirming that the document has been accurately and completely completed and that an audit trail and electronic signature information are available for review.
6) The Investigator will archive a copy of the case report forms (a PDF version of the eCRF reviewed by the Investigator) saved on CD-R or other media. eCRF provided in a viewable environment (access privileges to EDC system) will serve as copies from the time after electronic signature to the time the Investigator receives the CD-R or other recording media.
7) The Investigator will create a record explaining any case report form data that is

inconsistent with the source documents, submit the record to MTPC, and retain a copy.

18.4 Time of submission of Case Report Forms

The Investigator will fill out the eCRF and submit it to MTPC immediately after the observations and assessments of the subject have been completed.

19 DIRECT ACCESS TO SOURCE DATA

The Investigator and the head of the study site will accept monitoring and auditing by MTPC and inspections by the IRB and the regulatory authorities and will guarantee direct access to all data related to the study on these occasions.

20 STUDY QUALITY CONTROL AND QUALITY ASSURANCE

In order to maintain the quality and reliability of this study, the Medicago and MTPC implement "quality control of the study" and "quality assurance of the study" based on the SOP of the Medicago or MTPC. In addition, the study sites and the investigators must cooperate with the Medicago and MTPC for the quality control and quality assurance of the study.

In the quality control of the study, the monitor, with direct access as appropriate, will ascertain that this study is conducted in compliance with the procedure for the study-related activities in each study site, the latest protocol, and GCP. The monitor will also ascertain that the accuracy and completeness of the recorded content of the CRF reported by the (sub)Investigator can be verified against the study-related records such as the source data.

In order to ensure that the study is conducted in compliance with the protocol and GCP, the auditor will perform auditing in accordance with the GCP Auditing SOP and ascertain that the appropriate quality control is being implemented.

21 ETHICS

21.1 Ethical Conduct of the Study

The study must be conducted in consideration of the principles grounded in the Declaration of Helsinki and in compliance with the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, GCP, and the protocol.

21.2 Institutional Review Boards

The IRB shall review the conduct and continuation of the study based on its ethical, scientific, medical, and pharmacological standpoints, considering the IB, protocol and ICF.

21.3 Protection of Subject Confidentiality

Subject enrollment and subject identification in the CRF shall be performed using subject identification codes. Persons involved in this study shall maintain the confidentiality of subjects in direct access to source documents, publications in medical journals, submission of data to regulatory authorities, related to the conduct of the study.

22 RETENTION OF RECORDS

22.1 Records Retained at Study Sites

The responsible person for storage designated by the head of the study site will retain all study-related documents and records to be maintained at the study site until the later of 1) or 2) below. If MTPC requires the study site to retain the records for a longer period of time, the study site will consult with MTPC regarding how long and how the records should be retained.

If the Sponsor decides not to attach documents regarding the clinical study results collected from the study to the approval application form, MTPC shall report this fact and the reason for it to the head of the study site in writing.

MTPC will notify the head of the study site in writing if MTPC or Medicago obtains the marketing approval of the investigational product, or decides to the discontinue its development.

1) The day of marketing approval of the investigational product (or the day of approval of the partial change of manufacturing and marketing of the investigational product in the case of an additional indication) (or the day 3 years after the day when notification is received that development is to be canceled or the study results will not be included in the marketing application);
2) The day 3 years after the discontinuation or completion of the study.

22.2 Records Retained at the Medicago and MTPC

Medicago and MTPC will retain all study-related documents and records to be maintained by Medicago and MTPC until the later date of 1) or 2) below:

1) The day 5 years after marketing approval for the investigational product is obtained (or the day of approval of the partial change of manufacturing and marketing of the investigational product in the case of an additional indication) (or the day 3 years after the decision to terminate development is made if development is terminated) or the end of reexamination
2) The day 3 years after the discontinuation or completion of the study

23 PAYMENTS

Monetary payments to the subjects and study sites will comply with a contract or written agreement the study site and MTPC.

24 COMPENSATION FOR INJURY AND INSURANCE

24.1 Compensation for Injury

If study-related injury occurs in subjects, except in the case that a causal relationship to the study is ruled out, the sponsor will provide appropriate compensation based on the standard specified by the sponsor [Compensation consists of medical expenses (self-pay), medical allowance, and compensation]. Subjects eligible for compensation will not be required to prove a causal relationship.

24.2 Insurance

Medicago will purchase insurance and take other necessary actions to ensure its ability to cover the expenses and compensation for subject injuries related to the study.

25 PUBLICATION POLICY

Medicago has the ownership of the information contained in the protocol, and the information will be provided to the study personnel, such as the (sub)Investigator, and the IRB, but except when needed for the conduct of the study, the information must not be disclosed to any third party without agreement by Medicago in writing.

When the information obtained from this study is externally published to professional societies by study personnel at the study sites such as the (sub)Investigator, prior consent from Medicago must be obtained.

Medicago may freely use the data obtained in the study for any purpose, including reporting to the regulatory authorities, ensuring appropriate use, or marketing.

26 REFERENCES

Baz M, Luke CJ, Cheng X, Jin H, Subbarao K. H5N1 vaccines in humans. Virus Res 2013;178:78-98. doi: 10.1016/j.virusres.2013.05.006.

Cohet C, Montplaisir J, Petit D, Quinn MJ, Ouakki M, Deceuninck G, et al. Applying the test-negative design to vaccine safety studies: risk of narcolepsy associated with A/H1N1 (2009) pandemic influenza vaccination in Quebec [abstract 713]. Pharmacoepidemiol Drug Saf 2015;24:406-407. doi: 10.1002/pds.

Cohet C, van der Most R, Bauchau V, Bekkat-Berkani R, Doherty TM, Schuind A, Tavares Da Silva F, Rappuoli R, Carcon N, Innis BL. Safety of AS03-adjuvanted influenza vaccines: A review of the evidence. Vaccine 2019;37(23):3006-3021. doi: 10.1016/j.vaccine.2019.04.048.

FDA. Guidance for Industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. 2007.

Garcon N, Vaughn DW, Didierlaurent AM. Development and evaluation of AS03, an Adjuvant System containing alpha-tocopherol and squalene in an oil-in-water emulsion. Expert Rev Vaccines 2012;11:349-366. doi: 10.1586/erv.11.192.

Jackson LA, Campbell JD, Frey SE, Edwards KM, Keitel QA, Kotloff KL, Berry AA, Graham I, Atmar RL, Creech CB, Thomsen IP, Patel SM, Gutierrez AF, Anderson EL, Sahly HM, Hill H, Noah DL, Bellamy AR. Effect of varying doses of a monovalent H7N9 influenza vaccine with and without AS03 and MF59 adjuvants on immune response: a randomised clinical trial. JAMA 2015;314:237-46. doi: 10.1001/jama.2015.7916.

Lansbury L, Smith S, Beyer W, Karamehic E, Pasic-Juhas E, Sikira H, Mateus A, Oshitani H, Zhao H, Beck CR, Nguyen-Van-Tam JS. Effectiveness of 2009 pandemic influenza A(H1N1) vaccines: a systematic review and meta-analysis. Vaccine 2017;35:1996–2006. doi: 10.1016/j.vaccine.2017.02.059.

Launay O, Duval X, Fitoussi S, Jilg W, Kerdpanich A, Montellano M, Schwarz TF, Watanveerade V, Wenzel JJ, Zalcman G, Bambure V, Li P, Caplanusi A, Madan A, Gillard P, Vaughn DW. Extended antigen sparing potential of AS03-adjuvanted pandemic H1N1 vaccines in children, and immunologic equivalence of two formulations of AS03-adjuvanted H1N1 vaccines: results from two randomised trials. BMC Infect Dis 2013;13:435. doi: 10.1186/1471-2334-13-435.

Law B, Sturkenboom M. Safety platform for emergency vaccines (SPEAC). D2.3 Priority list of adverse events of special interest: COVID-19. Report v1.1. 2020 Mar 5.

Law B, Sturkenboom M. Safety platform for emergency vaccines (SPEAC). D2.3 Priority list of adverse events of special interest: COVID-19. Report v2.0. 2020a May 25.

Leroux-Roels I, Borkowski A, Vanwolleghem T, Drame M, Clement F, Hons E, Devaster J-M, Leroux-Roels G. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet 2007;370:580–9. doi: 10.1016/s0140-6736(07)61297-5.

Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020a Mar 27. pii: S0163-4453(20)30116-X.

doi: 10.1016/j.jinf.2020.03.005.

Madan A, Collins H, Sheldon E, Frenette L, Chu L, Friel D, Drame M, Vaughn DW, Innis BL, Schuind A. Evaluation of a primary course of H9N2 vaccine with or without AS03 adjuvant in adults: a phase I/II randomized trial. Vaccine 2017;35:4621–8. doi: 10.1016/j.vaccine.2017.07.013.

Madan A, Ferguson M, Rheault P, Seiden D, Toma A, Friel D, Soni J, Li P, Innis BL, Schuind A. Immunogenicity and safety of an AS03-adjuvanted H7N1 vaccine in adults 65 years of age and older: a phase II, observer-blind, randomized, controlled trial. Vaccine 2017a;35:1865–72. doi: 10.1016/j.vaccine.2017.02.057.

Madan A, Ferguson M, Sheldon E, Segall N, Chu L, Toma A, Rheault P, Friel D, Soni J, Li P, Innis BL, Schuind A. Immunogenicity and safety of an AS03-adjuvanted H7N1 vaccine in healthy adults: a phase I/II, observer-blind, randomized, controlled trial. Vaccine 2017b;35:1431–9. doi: 10.1016/j.vaccine.2017.01.054.

McElhaney JE, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, Ruiz-Palacios GM, van Essen GA, Caplanusi A, Claeys C, Durand C, Duval X, Idrissi ME, Falsey AR, Feldman G, Frey SE, Galtier F, Hwang S-J, Innis BL, Kovac M, Kremsner P, McNeil S, Nowakowski A, Richardus JH, Trofa A, Oostvogels L, Influence65 study group. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis 2013;13:485-496. doi: 10.1016/S1473-3099(13)70046-X.

Montplaisir J, Petit D, Quinn MJ, Ouakki M, Deceuninck G, Desautels A, Mignot E, De Wals P. Risk of narcolepsy associated with inactivated adjuvanted AS03A/H1N1 (2009) pandemic influenza vaccine in Québec. PLoS One 2014;9(9):e108489. doi: 10.1371/journal.pone.0108489.

Nolan T, Izurieta P, Lee BW, Chan PC, Marshall H, Booy R, Drame M, Vaughn DW. Heterologous prime-boost vaccination using an AS03B-adjuvanted influenza A(H5N1) vaccine in infants and children < 3 years of age. J Infect Dis 2014;210(11):1800-10. doi: 10.1093/infdis/jiu359.

Vaughn DW, Seifert H, Hepburn A, Dewe W, Li P, Drame M, Cohet C, Innis BL, Fries LF. Safety of AS03-adjuvanted inactivated split virion A(H1N1)pdm09 and H5N1 influenza virus vaccines administered to adults: pooled analysis of 28 clinical trials. Hum Vaccin Immunother 2014;10(10):2942-57. doi: 10.4161/21645515.2014.972149.

Waddington CS, Walker WT, Oeser C, Reiner A, John T, Wilkins S, Casey M, Eccleston PE, Allen RJ, Okike I, Ladhani S, Sheasby E, Hoschler K, Andrews N, Waight P, Collinson AC, Heath PT, Finn A, Faust SN, Snape MD, Miller E, Pollard AJ. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ 2010;340:c2649. doi: 10.1136/bmj.c2649.

Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020 Mar 12. pii: S1201-9712(20)30136-3. doi: 10.1016/j.ijid.2020.03.017.

Yang WH, Dionne M, Kyle M, Aggarwal N, Li P, Madariaga M, Godeaux O, Vaughn DW. Long term immunogenicity of an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine in young and

elderly adults: an observer-blind, randomised trial. Vaccine 2013;31:4389-4397. doi: 10.1016/j.vaccine.2013.07.007.

Yin JK, Khandaker G, Rashid H, Heron L, Ridda I, Booy R. Immunogenicity and safety of pandemic influenza A (H1N1) 2009 vaccine: systematic review and meta-analysis. Influenza Other Respir Viruses 2011;5(5):299-305. doi: 10.1111/j.1750-2659.2011.00229.x.