Brief protocol title	CoV2-001
Formal protocol title	Multicenter, randomized, combined Phase I dose-escalation and Phase IIa double-blind, placebo-controlled study of the safety, tolerability, and immunogenicity of GLS-5310 DNA vaccine administered intradermally against SARS-CoV-2
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IND Protocol Number:	
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PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and receive approval or a favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

Investigator's printed name and signature	Date
	28 MAR 2022
Medical Monitor	Date

Protocol Number: CoV2-001
Version Number: 5.0 / Version Date: 28 MAR 2022

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CoV2-001: CLINICAL PROTOCOL SYNOPSIS

Study Title: Multicenter, randomized, combined Phase I dose-escalation and Phase IIa double-blind, placebo-controlled study of the safety, tolerability, and immunogenicity of GLS-5310 DNA vaccine administered intradermally against SARS-CoV-2

Number of study sites and Countries/Regions: 5, Korea

Number of study participants: 45 (Phase I), 120 (Phase IIa)

Study Phase: I / IIa

Study Type: Phase I: Dose-ranging

Phase IIa: Multi-center, Randomized, Double-blind, Placebo

Study Period: About 20 months from the date of approval of the clinical study by the Ministry of Food and Drug Safety and the Institutional Review Board

- Recruitment period for test subjects: about 5 months
- Clinical trial period for each subject: at least 48 weeks

Research Hypothesis: GLS-5310 DNA vaccine delivered intradermally (ID) with JM-11 will be safe, well-tolerated and that vaccination will elicit immune responses against SARS-CoV-2 vaccine antigens.

Primary study objectives– *Phase I & IIa*:

- Evaluate the safety and tolerability of GLS-5310 vaccine
- Determine post-vaccination binding antibody responses induced by GLS-5310 relative to treatment arm

Secondary study objectives– *Phase I & IIa*:

- Determine the T cell responses induced by GLS-5310
- Determine the neutralizing antibody response induced by GLS-5310

Exploratory study objectives:

Phase I exploratory objectives

- Determine IgG antibody responses after a single dose of vaccine related to treatment arm
- Determine whether passive transfer of human serum can protect against pulmonary infection from SARS-CoV-2 challenge in an animal infection model

Phase II exploratory objectives

- Determine the persistence of immune responses following vaccination with GLS-5310
- Determine the extent of immune boosting for participants who are seropositive at baseline following vaccination with GLS-5310

Primary study endpoints– *Phase I & IIa*:

- Evaluate the adverse events (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials)
- Determine of GMT and seroconversion rate of SARS-CoV-2 Spike and ORF3a protein specific binding antibody responses induced by GLS-5310 relative to treatment arm (Endpoint titer of binding antibody in serum at each timepoint)

Secondary study endpoints– *Phase I & IIa*:

- Determine the positive responder rate of T cell responses induced by GLS-5310 (Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint)
- Determine of GMT and positive responder rate of the neutralizing antibody response induced by GLS-5310 (plaque-reduction neutralizing titer in serum at each timepoint)

Exploratory study endpoints

Phase I

- Determine binding antibody responses after a single dose of vaccine related to treatment arm (Endpoint titer of binding antibody in serum at each timepoint)
- Determine whether passive transfer of human serum can protect against pulmonary infection from SARS-CoV-2 challenge in an animal infection model (Survival rate, blood and viral load measurement of major organs, pathological examination of respiratory/lung area, immunogenicity evaluation)

Phase IIa

- Determine the persistence of immune responses following vaccination with GLS-5310 (Endpoint titer of binding antibody in serum at each timepoint, Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint, plaque-reduction neutralizing titer in serum at each timepoint)
- Determine the extent of immune boosting for participants who are seropositive at baseline following vaccination with GLS-5310 (Endpoint titer of binding antibody in serum at each timepoint, Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint, plaque-reduction neutralizing titer in serum at each timepoint
- Determine whether immune responses to GLS-5310 of participants age 66-85 years differ from those age 65 years and younger.

Table S1: Dosing arms and treatment regimen

Study Phase	Study Arm	N	Route	GLS-5310 Dose	Vaccination schedule	Table of events
1	1a	15	ID	0.6 mg	0 – 8 weeks	S2
1	1b	15	ID	1.2 mg	0 – 8 weeks	S2
1	1c	15	ID	1.2 mg	0 – 12 weeks	S3
2	2a	40	ID	Placebo	0 – 8 weeks	S2
2	2b	80	ID	1.2 mg	0 – 8 weeks	S2

Study design:

This Phase I / IIa study will assess the safety, tolerability, and immunogenicity of GLS-5310 DNA vaccine.

The Phase I portion of this study is an open-label, dose escalation study to assess two dose levels of GLS-5310 DNA vaccine (0.6 and 1.2 mg) as part of two vaccination regimens (0-8 weeks and 0-12 weeks). After enrolling study arm 1a (0.6 mg), participants will be randomized to study arms 1b and 1c. GLS-5310 will be administered via intradermal (ID) injection using the Mantoux technique followed by suction applied over the vaccination site using the JM-11 device. The primary outcome measures are (1) the safety and tolerability of GLS-5310 given ID with JM-11 and (2) binding antibody responses elicited by vaccination. Secondary outcome measures are the (3) T cell responses elicited to vaccine antigens and (4) neutralizing antibody titers. Exploratory goals of the study are to determine the IgG antibody responses after a single vaccination relative to treatment arm and whether passive transfer of immune serum can protect animals from pulmonary disease.

Dose escalation within the Phase I portion of the study will occur as follows. Study arm 1a (0.6 mg per vaccination) will be vaccinated and followed to the Week 1 safety visit. If no vaccine-associated severe adverse events (SAEs) have been documented, then enrollment into study arms 1b and 1c (1.2 mg per vaccination) will occur in a randomized manner. Phase I subjects complete Visit 4, an interim analysis to evaluate safety and binding antibody response is performed. The assessment of adverse events is performed after visit 1 to study arm 1a. The interim analysis is performed after visit 4 for study arms 1a, 1b, and 1c of the Phase I, and after visit 4 for study arms 2a and 2b of the Phase IIa. In order to enter the Phase IIa, the seroconversion rate for the antibody binding between the study arms is >70%, and the incidence of serious adverse reactions (Grade 3 or higher) related to the investigational drug should be no more than 1 case. In addition, the safety and immunogenicity results are evaluated on the data and safety monitoring board (DSMB).

Escalation to Phase IIa will occur based on the interim analysis.

The Phase IIa portion of this study is designed as a randomized, double-blind, placebo-controlled study with only a single active study drug arm. Subjects will be randomized to receive either placebo or GLS-5310 vaccine in a 1:2 ratio. The primary and secondary goals of the Phase IIa study are the same as the Phase I study. Exploratory goals of the Phase IIa study are to determine the persistence of the immune response following vaccination with GLS-5310 and the extent of immune boosting for those who are enrolled and are seropositive at baseline. The study will be unblinded at the post-vaccination visit (study visit 4) at which time subjects will be informed of their treatment assignment. Subjects who were assigned to the placebo group will be offered to be vaccinated with GLS-5310. Subjects assigned to the placebo group who choose to be vaccinated with GLS-5310 will be followed for a year from 1st GLS-5310 vaccination (Table S4); subjects assigned to the placebo group but who decline vaccination with GLS-5310 will be followed for a year from study entry as per the original study protocol (Table S3).

Sub-studies

A sub-study will be included within the Phase IIa portion of CoV2-001 clinical trial.

Participants 66-85 years of age: 30 persons will be recruited into the study to examine whether immune responses in this age group are similar or different from those age 66-85 years of age.

The above subgroup will be randomized as part of the main study, and not separately randomized.

At randomization, the initial 5 subjects are set as the sentinel group to confirm the safety of the elderly group. When the sentinel group is vaccinated with the clinical trial drug, the vaccination is carried out at an interval of at least 24 hours between each subject. Five subjects aged 65 to 74 years will be enrolled as a sentinel group for the older age cohort. If there are no adverse drug reactions (ADRs) occurring within the 7 days after the first vaccination in the sentinel group, then enrollment into the older age cohort can proceed.

Study outcome will be based on the ITT analysis inclusive of all subgroups, however, subgroup analysis will be performed as above as an exploratory endpoint.

Sample size considerations:

For the Phase I study, the sample size of 15 participants per group will allow detection of an increase in adverse events of 13% with 88% statistical power using a 2-sided alpha of 0.10. The sample size will allow assessment of a difference of 35% in seroconversion between groups after a complete vaccination series or after a single vaccination at a similar statistical power. The sample size will also allow assessment of a difference in geometric mean titers by ELISA, determined by analysis of variance, between dose levels (low dose versus high dose) of 35% with 86% statistical power at an alpha of 0.10. These results will be used to guide selection of vaccination regimen for Phase IIa.

For the Phase IIa study, the sample size of 300 participants, randomized 2:1 vaccine to placebo will allow detection of a difference in adverse events of 18% with 82% statistical power at alpha of 0.05. The sample size will allow assessment of a difference in seroconversion between groups of at least 10% with greater than 95% statistical power at alpha of 0.05. For a sample size of 126 participants, randomized 2:1 vaccine to placebo will yield 80% probability to detect a difference in the rate of adverse events of 28% or greater. A sample size of N=126 will allow detection of a difference in seroconversion of 14% with 80% statistical power. Safety and immunogenicity will be determined at planned Interim Analysis and after all vaccinations are completed.

Safety assessments:

Participants will be monitored at each study visit for adverse events. Laboratory safety assessments will be performed as indicated in the schedule of events to determine whether there are any changes in hematologic parameters, electrolytes, or renal function relative to pre-vaccination assessment. Subjects administered GLS-5310 will be followed for a year from their first vaccination with GLS-5310 regardless of initial study arm randomization. In the Phase IIa study, subjects, will be followed for 48 weeks from first vaccination, however, subjects assigned to placebo and who chose to be vaccinated with GLS-5310, will be followed for a year from first vaccination with GLS-5310 or a total of 60 weeks.

Immunogenicity analysis:

This study is not powered to determine efficacy of the vaccine to prevent SARS-CoV-2 disease. The study is, however, powered to assess whether the vaccine can induce immune responses. Immunogenicity assessments will measure binding antibodies by ELISA; neutralizing antibodies by either live virus PRNT, pseudovirus assay, or binding inhibition assay; and T cell cellular responses by ELISPOT.

Inclusion criteria:

1. Age greater than 19 to 85 years of age (Phase I will be restricted to an upper age limit of 50 years of age); Phase IIa will allow enrollment of 30 persons 66 to 85 years of age.
2. Able to provide informed consent
3. Able and willing to comply with study procedures
4. For women of childbearing potential, able and willing to use an approved form of pregnancy prevention through to 4 weeks post boost vaccination

Exclusion criteria:

1. Current or planned pregnancy through to 4 weeks post-boost vaccination for women of childbearing potential
2. Currently breastfeeding
3. Current or past participation in a coronavirus (MERS-CoV, SARS-CoV-2) vaccine study
4. Administration of an investigational agent within 6 months of the 1st dose
5. Administration of a vaccine within 28 days prior to the 1st dose
6. Administration of immune globulin or blood-derived medicinal product within 16 weeks of enrollment
7. Administration of an anti-TNFα inhibitor such as infliximab, adalimumab, etanercept, or anti-CD20 monoclonal antibody rituximab within 24 weeks from enrollment
8. Current daily treatment of systemic corticosteroids of 20 mg of prednisone or greater, dexamethasone of 3 mg or greater; or the equivalent dose of other systemic corticosteroids
9. Administration of any Immunosuppressive Drug or Immunomodulator within 3 months of the 1st dose
10. History of bone marrow transplantation
11. Current or planned chemotherapy treatment for hematologic or solid tumor during study period or treatment during the 5 years prior to enrollment
12. Respiratory disease (ex. Asthma, Chronic obstructive lung disease) that is uncontrolled per their treating physician
13. Cardiovascular disease (ex. myocardial ischemia, congestive heart failure, cardiomyopathy, clinically significant arrhythmia) that is uncontrolled per their treating physician
14. Uncontrolled Hypertension (Systolic pressure >150mmHg or Diastolic pressure >95mmHg)
15. Uncontrolled Diabetes
16. Severe allergic reaction or anaphylactic reaction after vaccination in the past
17. Immunosuppresion including immunodeficiency disease or family history
18. Positive of serum test at screening of Hepatitis B surface antigen, Hepatitis A IgM, HIV, or Hepatitis C. Persons who are Hepatitis C seropositive, and for whom an HCV RNA test is negative, are allowed into the study.
19. Baseline screening lab(s) with Clinically Significant abnormality (Grade 2 or higher)
20. Serious adverse reaction to a drug containing Investigational Product (GLS-5310) or other ingredients of the same categories or to a vaccine or antibiotic, nonsteroidal anti-inflammatory disease control, etc. or an allergic history
21. History of hypersensitivity to vaccination such as Guillain-Barre syndrome
22. History of PCR-confirmed infection with SARS-CoV-2 or positive SARS-CoV-2 antibody or PCR test at screening
23. Subjects who have been contact with COVID-19 infections in the past prior to administration, have been classified as COVID-19 confirmed patients, medical patients or patients with symptoms or have been identified with SARS and MERS infection history in the past
24. Acute over 37.5℃ fever, cough, difficulty breathing, chills, muscle aches, headache, sore throat, loss of smell, or loss of taste within 72 hours prior to administration
25. Healthcare workers participating in the medical examination of patients infected with COVID-19 or high-risk individuals who are likely to be occupationally exposed to SARS-CoV-2
26. Not willing to allow storage and future use of samples for SARS-CoV-2 related research
27. Prisoner or subjects who are compulsorily detained for treatment of a psychiatric illness
28. Any illness or condition that, in the opinion of the investigator, may affect the safety of the subject or the evaluation of a study endpoint

29. Receipt of a vaccine to prevent COVID-19 infection

Safety evaluation analysis method: Adverse events occurring after vaccination are summarized according to frequency, and presented according to SOC and PT along with the number and ratio of subjects with adverse events. The continuous response variable at each time point and the change from baseline are summarized as mean, median, minimum and maximum values. Categorical response variables are summarized as a percentage for each time point.

Data for the Phase IIa study will be unblinded after database lock for analysis. Since subjects who were randomized to placebo will have the opportunity to be given the vaccine, safety assessments can be divided into 3 groups:

1) Randomized to vaccine
2) Randomized to placebo
3) Subset of Placebo subjects who received vaccine after unblinding

Safety comparison will be made based on the randomization allocations and separately on the placebo randomized subject who rolled over to vaccine. These 2 vaccine groups will not be pooled.

Immunogenicity evaluation analysis method: Although this clinical trial has no statistical power to evaluate the effectiveness of a vaccine for preventing disease against SARS-CoV-2, the immune response induced by the vaccine can be evaluated by a statistical analysis. Immunogenicity results are classified as responders/non-responders and are expressed as the frequency of each assay response for each group at each time point where the evaluation is performed. The proportions of the differences between each group and an estimate of the correct 95% binominal and 95% confidence intervals are calculated. Since phase 1 clinical trials cannot secure sufficient power between administration regimens, comparisons between groups are analyzed using Fisher's Exact Test.

Similar to the safety assessments, subject who were randomized to receive Placebo who then received vaccines after the study was unblinded will be followed for immunogenicity. Results of this group will not be compared to the randomized vaccine group or pooled with the original randomized vaccine group results.

Table S2: Schedule of Events (Vaccinations at 0 and 8 weeks)

Tests and Observations	**Visit 1**	**Visit 2**	**Visit 3**	**Tele Visit**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Un-sched**
Time relative to enrollment	Screen Enroll	Wk 1	Wk 8	Wk 9	Wk 12	Wk 16	Wk 24	Wk 36	Wk 48	N/A
Permitted window (days)		±2d	±3d	±3d	±3d	±4d	±7d	±7d	±7d	N/A
Clinical Evaluations										
Review Record Prior and Concomitant Meds	X	X	X		X	X	X	X	X	X
Physical Exam and Vital Signs [2]	X	X	X		X	X	X	X	X	X
Safety Evaluations*										
Record Adverse Events	X	X	X	X	X	X	X	X	X	X
Examine injection site and record findings	X	X	X	X	X					X
Blood for Hematology [3]: CBC with differential	X	X			X				X	
Blood for Chemistry Testing [4]: Sodium, potassium, glucose, BUN, Cr, ALT, Bili	X	X			X				X	
Serological test [5]	X									
Record most recent HgbA1c (diabetics only) [6]	X									
Chest X-ray	X									
12-lead ECG	X									
PCR or Antibody test for SARS-CoV-2	X									
Urine for pregnancy testing (as applicable)	X		X							
Study Related Procedures										
Administer study drug	X		X							
Subject Diary [7]	X	X [7]	X		X [7]	X	X			
VAS Score	X		X		X	X				
Collect blood for serum [8]	X		X		X	X	X	X	X	
Collect blood for PBMCs [9]	X		X		X	X	X	X	X	
Estimated blood volume										
Maximum blood volume collected	60	10	50		60	50	50	50	60	

* If there are test results for safety evaluation items within 1 week from the first investigational product vaccination date, it can be used

Check the occurrence of adverse events by telephone.

1 Written Informed Consent must be obtained PRIOR to any study procedures; document that a completed copy has been provided to participant.

2 At enrollment, a full physical exam is performed; height and weight are recorded. At follow-up and unscheduled visits, only a targeted physical exam is performed determined by the presence of symptoms and directed to those organ systems only.

3 Blood for Hematology: RBC, hemoglobin, hematocrit, platelet, WBC, neutrophil, lymphocyte, monocyte, eosinophil, basophil

4 Blood for Chemistry Testing: Sodium, potassium, glucose, BUN, Cr, ALT, Bili, Ca, Cl, AST, ALP, CPK, albumin, total protein, total cholesterol

5 Serological test: Hepatitis B (HBsAg), Hepatitis A (IgG and IgM), HIV, Hepatitis C- HCV RNA testing, if necessary)

6 Obtain HgbA1c if test result within past 3 months is not available

7 Subject diary their responses up to 7 days after vaccination of the investigational product on the clinical trial-related record sheet distributed to the investigator. Diaries are collected and reviewed at indicated visits

8 For serum, collect 1 x 10 mL red top or serum separator tubes;

9 For PBMCs, collect 4 x 10 mL ACD tubes;

Table S3: Schedule of Events (Vaccinations at 0 and 12 weeks, Phase 1 study ONLY)

Tests and Observations	**Visit 1**	**Visit 2**	**Visit 3**	**Telephone Visit 1#**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Unscheduled**
Time relative to enrollment	Screen, Enroll	Week 1	Week 12	Week 13	Week 16	Week 20	Week 24	Week 36	Week 48	N/A
Permitted window (days)		±2d	±3d	±3d	±3d	±4d	±7d	±7d	±7d	N/A
Clinical Evaluations										
Obtain Informed Consent [1]	X									
Review Eligibility Criteria	X									
Review and Record Medical History	X									
Review and Record Demographics	X									
Review Record Prior and Concomitant Meds	X	X	X		X	X	X	X	X	X
Physical Exam and Vital Signs [2]	X	X	X		X	X	X	X	X	X
Safety Evaluations										
Record Adverse Events	X	X	X	X	X	X	X	X	X	X
Examine injection site and record findings	X	X	X	X	X					X
Blood for Hematology [3]: CBC with differential	X	X			X				X	
Blood for Chemistry Testing [4]: Sodium, potassium, glucose, BUN, Cr, ALT, Bili	X	X			X				X	
Serological test [5]	X									
Chest X-ray	X									
12-lead ECG	X									
PCR or Antibody test for SARS-CoV-2	X									
Urine for pregnancy testing (as applicable)	X		X							
Study Related Procedures										
Administer vaccine	X		X							
Subject Diary [6]	X	X [7]	X		X [7]					
VAS Score	X		X							
Collect blood for serum [8]	X		X		X	X	X	X	X	
Collect blood for PBMCs [9]	X		X		X	X	X	X	X	
Estimated blood volume										
Maximum blood volume collected	80	10	70		80	70	70	70	80	

Check the occurrence of adverse events by telephone.

1 Written Informed Consent must be obtained PRIOR to any study procedures; document that a completed copy has been provided to participant.

2 At enrollment, a full physical exam is performed; height and weight are recorded. At follow-up and unscheduled visits, only a targeted physical exam is performed determined by the presence of symptoms and directed to those organ systems only.

3 Blood for Hematology: RBC, hemoglobin, hematocrit, platelet, WBC, neutrophil, lymphocyte, monocyte, eosinophil, basophil

4 Blood for Chemistry Testing: Sodium, potassium, glucose, BUN, Cr, ALT, Bili, Ca, Cl, AST, ALP, CPK, albumin, total protein, total cholesterol

5 Serological test: Hepatitis B, Hepatitis A, HIV, Hepatitis C

6 Subject diary their responses up to 7 days after vaccination of the investigational product on the clinical trial-related record sheet distributed to the investigator.

7 The investigator collects and reviews the records related to the clinical trial.

8 For serum, collect 1 x 10 mL red top or serum separator tubes;

9 For PBMCs, collect 4 x 10 mL ACD tubes;

Table S4: Schedule of Events (Phase IIa subjects assigned to the placebo group who choose to be vaccinated with GLS-5310 at study visit #4: Vaccinations at 0 and 8 weeks)

Tests and Observations	**Visit 1**	**Visit 2**	**Visit 3**	**Tele Visit**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Un-sched**
Time relative to enrollment	Screen Enroll	Wk 1	Wk 8	Wk 9	Wk 12	Wk 20	Wk 24	Wk 36	Wk 48	N/A
Permitted window (days)		±2d	±3d	±3d	±3d	±4d	±7d	±7d	±7d	N/A
Clinical Evaluations										
Obtain Informed Consent [1]	X									
Review Record Prior and Concomitant Meds	X	X	X		X	X	X	X	X	X
Physical Exam and Vital Signs [2]	X	X	X		X	X	X	X	X	X
Safety Evaluations*										
Record Adverse Events	X	X	X	X	X	X	X	X	X	X
Examine injection site and record findings	X	X	X	X	X					X
Blood for Hematology [3]: CBC with differential	X	X			X				X	
Blood for Chemistry Testing [4]: Sodium, potassium, glucose, BUN, Cr, ALT, Bili	X	X			X				X	
Serological test [5]	X									
Record most recent HgbA1c (diabetics only) [6]										
Chest X-ray	X									
12-lead ECG	X									
PCR or Antibody test for SARS-CoV-2	X									
Urine for pregnancy testing (as applicable)	X		X							
Study Related Procedures										
Administer study drug	X		X							
Subject Diary [7]	X	X [7]	X							
VAS Score	X		X		X	X				
Collect blood for serum [8]	X		X		X	X	X	X	X	
Collect blood for PBMCs [9]	X		X		X	X	X	X	X	
Estimated blood volume										
Maximum blood volume collected	60	10	50		60	50	50	50	60	

* If there are test results for safety evaluation items within 1 week from the first investigational product vaccination date, it can be used

Check the occurrence of adverse events by telephone.

1 Written Informed Consent must be obtained PRIOR to any study procedures; document that a completed copy has been provided to participant.

2 At enrollment, a full physical exam is performed; height and weight are recorded. At follow-up and unscheduled visits, only a targeted physical exam is performed determined by the presence of symptoms and directed to those organ systems only.

3 Blood for Hematology: RBC, hemoglobin, hematocrit, platelet, WBC, neutrophil, lymphocyte, monocyte, eosinophil, basophil

4 Blood for Chemistry Testing: Sodium, potassium, glucose, BUN, Cr, ALT, Bili, Ca, Cl, AST, ALP, CPK, albumin, total protein, total cholesterol

5 Serological test: Hepatitis B (HBsAb, HBsAg), Hepatitis A (IgG, IgM), HIV, Hepatitis C- HCV RNA testing, if necessary

6 HgbA1c is performed if not available within 3 months prior to enrollment

7 Subject diary their responses up to 7 days after vaccination of the investigational product on the clinical trial-related record sheet distributed to the investigator. Diaries are reviewed at the relevant visits in the schedule.
8 For serum, collect 1 x 10 mL red top or serum separator tubes;
9 For PBMCs, collect 4 x 10 mL ACD tubes;

[Abbreviations and Terms]

Abbreviations	Terms
ACE2	Angiotensin converting enzyme 2 (receptor binding protein)
AE	Adverse event
ALT	Alanine aminotransferase
BAL	Bronchoalveolar lavage
BUN	Blood urea nitrogen
CBC	Complete blood count
COPD	Chronic obstructive pulmonary disease
eCRF	Electronic case report form
EDC	Electronic data capture
ERER	Event requiring expedited reporting
GMT	Geometric mean titer
HBV	Hepatitis B virus
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ID	Intradermal
IFNγ	Interferon gamma
IM	Intramuscular
IRB	Investigation review board
ITT	Intention-to-treat
IUD	Intrauterine device
M	Membrane protein
MERS-CoV	Middle East respiratory syndrome coronavirus
mITT	Modified intention-to-treat
NK	Natural killer
NP	Nucleocapsid protein
NS	Not stated
PBMCs	Peripheral blood mononuclear cells
PHI	Personal health information

Abbreviations	Terms
PI	Principal investigator
PID#	Participant identification number
PP	Per-protocol
PRNT	Plaque reduction neutralization titer
PT	Preferred term
RBD	Receptor binding domain
S	Spike (coronavirus spike protein)
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus, type 2
SOC	System organ class
SS	Safety set
SSC	Saline sodium citrate
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

1. INTRODUCTION

This Phase I / II study will examine the safety, tolerability and immunogenicity of the GLS-5310 DNA vaccine against the Severe Acute Respiratory Syndrome coronavirus, type 2 (SARS-CoV-2) when administered intradermally (ID) with the JM-11 device to healthy individuals without a history of documented SARS-CoV-2 infection.

1.1 Background and Rationale

SARS-CoV-2 is the third highly pathogenic coronavirus identified to cause disease in humans since 2002. SARS-CoV caused a total of approximately 10,000 cases worldwide between 2002 and 2003 with a global mortality rate of 10%. The Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012 and has resulted in fewer than 3,000 cases worldwide but with a mortality rate of 36%.

SARS-CoV-2 emerged in the last months of 2019. as of October 2020 Global case rates have exceeded 40 million with greater than 1 million deaths. Many countries are currently experiencing a 2nd wave of infection with increasing case rates, hospitalizations, and death rates.

Currently, greater than 200 vaccine candidates against SARS-CoV-2 have been developed with a number advanced to clinical trials [1]. Approximately 10 vaccines have been granted emergency use authorization in multiple countries. The vast majority of vaccine candidates specifically target the coronavirus spike (S) protein [2,3], while others are versions of inactivated viruses and target the entire virus [4].

1.1.1 The SARS-CoV-2 Spike protein as a vaccine target

The coronavirus S protein has been the dominant antigenic target for SARS-CoV, MERS-CoV, and SARS-CoV-2 vaccine design. Our MERS-CoV DNA vaccine, GLS-5300, also targets the S protein and has been shown to induce strong antibody and T cell responses in healthy adults [5 6]. Similarly, most of the SARS-CoV-2 vaccine candidates in pre-clinical and clinical development have targeted the coronavirus S protein as a single antigen.

Previous studies of SARS-CoV vaccine constructs in pre-clinical studies, summarized in the GLS-5310 Investigator's Brochure (IB), showed that S-only vaccines were in general not able to induce sterilizing immunity in animal models of infection. A similar phenomenon was seen for MERS-CoV vaccines. SARS-CoV-2 vaccines in development have also shown variable ability to induce sterilizing immunity. Rhesus macaques inoculated with the ChAdOx1 vaccine encoding the SARS-CoV-2 S protein developed less clinical disease, however, an equal number of animals in the vaccine and control groups demonstrated high pulmonary viral load levels [2]. In this same study, nasal RNA viral loads did not differ between vaccinated and control animals. A separate research group evaluated a series of S protein DNA vaccines [7]. While these vaccine constructs induced high levels of neutralizing antibodies and T cell responses in Rhesus macaques, bronchoalveolar lavage (BAL) samples showed continued viral presence and thus demonstrated that non-sterilizing immunity was obtained in 50-75% of animals [7]. Nasal swabs from vaccinated animals evaluated for the presence of virus showed no difference from control animals. Antibodies from vaccinated animals induced antibody dependent neutrophil or NK, or monocyte phagocytosis. However, whether this phenomenon correlated with greater viral survival and/or correlated with any clinical signs was not reported [7]. Finally, an inactivated SARS-CoV-2 vaccine induced high levels of binding and neutralizing antibodies in rats and macaques [4]. Macaques demonstrated

dose-dependent protection such that animals receiving 3 μg of vaccine had low levels of virus in the lung, whereas those inoculated with 6 μg had no detectable virus in the lung, however, virus was present in throat swabs regardless of high and low-dose [4]. Importantly, vaccinated animals still developed moderate pulmonary inflammation on histology [4].

The coronavirus nucleocapsid (N) protein is also very immunogenic with high levels of antibody and T cell responses seen among patients recovered from infection. Moreover, cellular responses against the SARS-CoV N have been found to be persistent over years. However, inclusion of N as a vaccine antigen may be contraindicated as SARS-CoV vaccines that included this protein induced significant immune priming resulting in an intense eosinophilic pneumonitis whereas the viral S did not [8,9]. A commentary by Hotez *et al*. cited the N as the inciting antigenic target inducing a Th17 immune response leading to immune priming [10]. Consensus recommendations of the Coalition for Epidemic Preparedness and Innovation (CEPI) and the World Health Organization (WHO) similarly recommend avoidance of the SARS-CoV-2 N in vaccine constructs [11].

To summarize, while the SARS-CoV-2 S protein is an appealing target, it may not induce sterilizing immunity when used as a sole vaccine antigen and inclusion of the coronavirus N protein may be contraindicated in a vaccine. In the next section we discuss our rationale and the merits of including ORF3a as a second vaccine antigen.

1.1.2 The SARS-CoV-2 ORF3a protein as a vaccine antigenic target

Studies of patients recovered from SARS-CoV infection have shown good correlation between the presence of binding and neutralizing antibodies [12]. Antibodies against the SARS-CoV S protein were relatively short-lived with a half-life of about 6 weeks and a decay more rapid in those with more severe disease [12]. In contrast, T cell responses were persistent and long-lived to at least 4 years with the greatest magnitude of responses against the replicase, S, ORF3a, ORF7, and NP [13]. T cell responses against the S, ORF3, membrane (M), and S were the most prevalent among convalescent patients. A DNA vaccine against the SARS-CoV ORF3a was shown to be safe and able to induce high levels of humoral and cellular immune responses in mice [14].

For SARS-CoV-2, both S and ORF3a have similarly been shown to be potent inducers of T cell responses in recovered patients [15], and its inclusion in our vaccine is primarily as a second immunogen to strengthen the overall T cell response. Importantly, T cell responses against S and ORF3a were the most prevalent among patients recovered from natural SARS-CoV-2 infection and reactivity was observed among the HLA-restricted epitopes that are most prevalent in the US and Korean populations [16].

In addition to the lack of sterilizing immunity induced by S protein vaccines, a number of recent reports raise additional potential concerns as to the reliance on vaccines that only target the S protein. A novel S mutation, D614G, that has been identified among persons infected with SARS-CoV-2 enhances viral infectivity and is associated with the loss of neutralizing activity in approximately 7% of such individuals [17]. Second, the SARS-CoV-2 S protein has been shown to undergo conformational changes within the acidic environment of endosomes, which abolishes the effects of bound neutralizing antibodies [18] – thus raising the concern that neutralizing antibodies may be ineffective or less effective than predicted by *in vitro* assays.

Finally, antibodies against SARS-CoV-2 decline quickly after infection, often becoming undetectable in as short as 90 days post-infection [19], suggesting the need for T cell immunogenicity for a long-lasting effect. Two recent studies provide critical evidence that ORF3a is a major immunogen of SARS-CoV-2 within the immediate period post-infection [15,16]. T cell

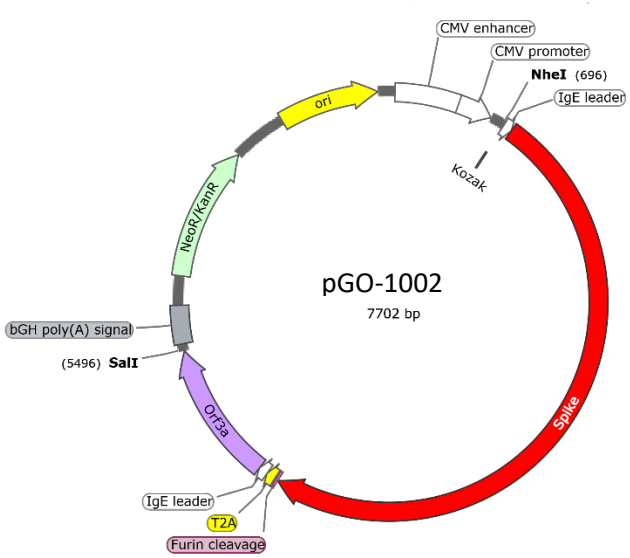
responses against ORF3a were present in 80-100% of sampled convalescent individuals [16]. Perhaps even more critical is that only S and ORF3a contained HLA A*02:01 and A*24:02 restricted epitopes, highly prevalent HLA haplotypes in the US and Korea [20].

The GLS-5310 vaccine was designed to target the S and ORF3a viral antigens of SARS-CoV-2 to generate robust immune responses from both B and T cells that may work synergistically to increase vaccine effectiveness. Pre-clinical studies of GLS-5310 are detailed in the IB. Pre-clinically, we have shown that each antigen is independently expressed from our DNA plasmid vaccine construct *in vitro*, and together are immunogenic *in vivo* with each inducing strong B and T cell immune responses, including high levels of binding and neutralizing antibodies, following intradermal administration of GLS-5310 with the JM-11device. Moreover, pre-clinical data has demonstrated immune responses equal to or greater than those elicited with use of electroporation.

1.2 Investigational Agent

GLS-5310 DNA plasmid vaccine contains a single plasmid, pGO-1002 (Figure 1.2-1), formulated at 6 mg/ml in 1X saline sodium citrate (SSC) buffer.

Figure 1.2-1: pGO-1002 plasmid



1.3 Dose and Regimen Rationale

For this Phase I / II study, GLS-5310 will be given at one of two dose levels (0.6 mg and 1.2 mg) administered intradermally (ID) by injection followed by suction using the JM-11device. Vaccine will be administered at baseline and again at either 8 or 12 weeks.

First of all, the factors to consider for setting the capacity are as follows.

The DNA vaccine is not directly vaccinated with a viral antigen that induces a vaccine immune response, but if it is vaccinated in the form of DNA, which is a gene encoding the antigen, it is delivered into cells, and then the antigen is produced and secreted from the DNA through transcription and translation processes. Therefore, the immune response of the vaccine does not increase directly in proportion to the administered dose. Therefore, rather than setting the clinical dose through animal experiments like the existing vaccine, the standard dose is set in consideration of the administration route based on the final concentration of the manufactured

DNA vaccine, and the optimal dose is increased or decreased through clinical trial. It is common to find. For example, the maximum concentration of our DNA vaccine is 6-10mg/mL, and in general, the intramuscular vaccination volume is 1mL and the intradermal vaccination volume is 0.1mL. Applying this, the standard dose for clinical trials is 6-10 mg dose for intramuscular vaccination, and 0.6 to 1.0 mg dose for intradermal vaccination.

The dose levels chosen are consistent with the dosage range for our prior MERS-CoV DNA plasmid vaccine, GLS-5300, studies, and the above contents. In the Phase I study of GLS-5300, vaccine was administered IM at doses of either 0.6, 2, or 6 mg (NCT02670127 [5]) and in the Phase Ib/IIa study GLS-5300 was administered ID at doses of either 0.3 or 0.6 mg (NCT03721718 [6]). Results of these two studies demonstrated no clear dose effect for the GLS-5300 vaccine given over a 10-fold range from 0.6 mg to 6 mg. In addition, as a result of pre-clinical efficacy evaluation of GLS-5310, the level of vaccine immune response induced by the use of an electroporator and a suction was similar. Therefore, although the clinical study of the MERS DNA vaccine used electroporation, it can be used as the basis for the dose setting of the GLS-5310 clinical study. Therefore, when the maximum concentration of the drug product of GLS-5310 is 6mg/mL and 0.1mL, which is the volume for intradermal vaccination, is applied, the standard dose becomes 0.6mg. The second dose was set to a 1.2mg dose, which was doubled from the 0.6mg dose, using the results of the clinical study of the MERS DNA vaccine, and the optimal dose will be selected through a phase 1 study of this clinical trial protocol.

To select the vaccination interval of GLS-5310, an interim analysis of the phase 1/2a clinical study of the MERS DNA vaccine (GLS-5300) was performed. The immune responses in the 3 times vaccination group (0-4-12 weeks) and the 2 times vaccination group (0-8 weeks) were compared. The binding antibody titers and neutralizing antibody titers at the time point of 8 weeks (after the second dose and after the first dose, respectively) of the 3 times vaccination group and the 2 times vaccination group were similar. At 12 weeks (all after the second dose), the 2 times vaccination group was rather higher.

As a result, in the case of DNA vaccine, it was confirmed that setting the interval between single vaccination and 2 times vaccination of 8 weeks or more could induce a more effective vaccine immune response, and this was applied to GLS-5310 vaccine.

1.3.1 Function of Suction after intradermal administration of DNA vaccine

For the purpose of researching gene therapy products, when a plasmid, a naked DNA encoded with a target gene, was administered in the body and then suction, the result of protein expression from the target gene at that injection site has been studied and published several times. At this time, the plasmid itself can be delivered intracellularly when administered into the human body, but when suction is applied, it can be seen that it induces physical stimulation at the injection site of administration and affects gene expression in the plasmid. The suction device is an industrial product device for beauty or an equivalent or higher device that simply applies suction pressure.

The main component of DNA vaccines is a plasmid containing a gene encoding an antigen of a virus that causes disease. When the DNA vaccine is administered intradermally, the vaccine

immune response is induced by antigens generated from the DNA vaccine. At this time, when the inhalation pressure used in the gene therapy research is applied, it provides a physical stimulation to the intradermal cells at the injection site, thereby giving a secondary effect of enhancing the vaccine immune response.

1.4 Risk/Benefit Assessment

In accordance with the International Conference on Harmonization (ICH), this study has been designed to minimize the risk to study participants.

This study of GLS-5310 vaccine is designed to determine whether the vaccine can induce immune responses in an effort to prevent disease from SARS-CoV-2. The adverse effects of GLS-5310 vaccine are unknown, however, GLS-5310 is similar to other GeneOne Life Science vaccines. These include Phase I and Phase Ib/IIa studies of GLS-5300 DNA vaccine against MERS-CoV. Results of the Phase I study of GLS-5300 have been published [5] with no vaccine associated serious adverse events (SAEs) and most common adverse events (AEs) were related to electroporation-based administration. Preliminary results of the GLS-5300 Phase Ib/IIa study were presented at the May 2020 meeting of the American Society for Gene and Cell Therapy [6] with no vaccine associated SAEs. Treatment assignment will be unblinded at visit 4 and participants and site personnel informed of vaccine or placebo status. Subjects that had been assigned to placebo will be offered vaccination with GLS-5310 clinical trial drugs. However, the information on safety and efficacy may be limited if an approved or an emergency use authorized vaccine is administered after vaccination of the clinical trial study drug.

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

GLS-5310 DNA vaccine administered ID will be well tolerated and will elicit immune responses against the SARS-CoV-2 vaccine antigens.

2.2 Primary Objectives and Outcome Variables – *Phase I & II*

- Evaluate the safety and tolerability of the GLS-5310 DNA vaccine delivered ID
- Determine the post vaccination binding antibody responses induced by GLS-5310 DNA vaccine

2.3 Secondary Objectives and Outcome Variables – *Phase I & II*

- Determine the T cell responses induced by GLS-5310 DNA vaccine
- Determine the neutralizing antibody response induced by GLS-5310
- For those with incident SARS-CoV-2 infection, determine the difference in moderate or severe pulmonary disease relative to treatment group

2.4 Exploratory Objectives

Phase I exploratory objectives

- Determine IgG antibody responses after a single dose of vaccine related to treatment arm
- Determine whether passive transfer of human serum following ID vaccine administration can protect against pulmonary infection from SARS-CoV-2 challenge in an animal infection model

Phase II exploratory objectives

- Determine the persistence of immune responses following vaccination with GLS-5310 in long-term follow-up visits
- Determine the extent of immune boosting responses for participants who are seropositive at baseline following vaccination with GLS-5310
- Determine whether immune responses to GLS-5310 of participants age 66 to 85 years differ from those age 65 years and younger.

3. STUDY DESIGN

This Phase I / II study will assess the safety, tolerability, and immunogenicity of GLS-5310 DNA vaccine.

The Phase I study is an open-label, dose escalation study to assess two dose levels of GLS-5310 DNA vaccine (0.6 and 1.2 mg) and given via two vaccination regimen (0-8 weeks and 0-12 weeks). Participants will be randomized to one of the three treatment arms. GLS-5310 will be administered via intradermal (ID) injection using the Mantoux technique followed by suction applied over the vaccination site using the JM-11device. The primary outcome measures are the safety and tolerability of GLS-5310 given ID with JM-11 and binding antibody responses elicited by vaccination. Secondary outcome measures are the T cell responses elicited to vaccine antigens and neutralizing antibody titers.

Dose escalation within the Phase I portion of the study will occur as follows. Study arm 1a (0.6 mg per vaccination) will be vaccinated and followed to the Week 1 safety visit. If no vaccine-associated severe adverse events (SAEs) have been documented, then enrollment into study arms 1b and 1c (1.2 mg per vaccination) will occur in a randomized manner. An interim analysis will occur after visit 4, four weeks after the 2nd vaccination to assess safety and binding antibody responses. Escalation to Phase II will occur based on this analysis. The choice of regimen for the Phase II study will be determined after review of study objectives.

The Phase IIa study is designed as a randomized, double-blind, placebo-controlled study with only a single active study drug arm. Subjects will be randomized to receive either placebo or GLS-5310 vaccine in a 1:2 ratio. The primary and secondary goals of the Phase II study are the same as the Phase I study. An interim analysis will be performed at Visit 4, one month after the final vaccination. The study will be unblinded at the post-vaccination visit (study visit 4) at which time subjects will be informed of their treatment assignment. Subjects who were assigned to the placebo group will be offered to be vaccinated with GLS-5310. Subjects assigned to the placebo group who choose to be vaccinated with GLS-5310 will be followed for a year from 1st GLS-5310 vaccination (Table S4); subjects assigned to the placebo group but who decline vaccination with GLS-5310 will be followed for a year from study entry as per the original study protocol.

[Sub-studies]

A sub-study will be included within the Phase IIa portion of CoV2-001 clinical trial.

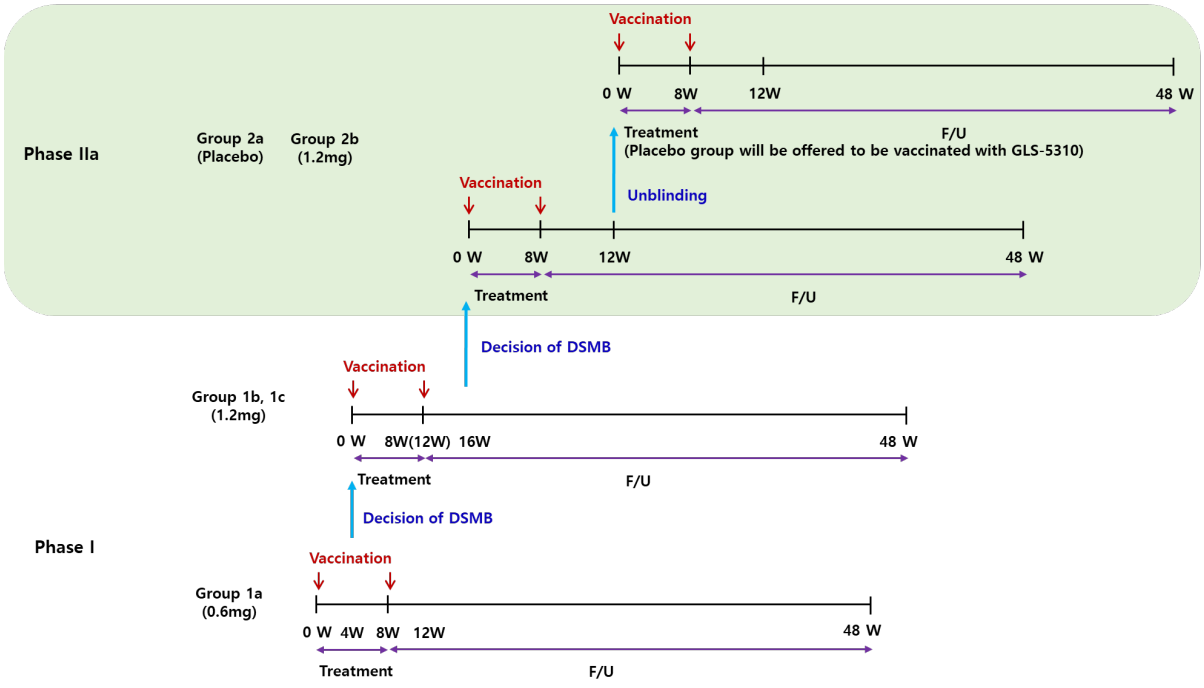
Participants > 66-85 years of age: up to 30 persons will be recruited to examine whether immune responses in this age group are similar or different from those age < 66-85 years of age.

The above subgroup will be randomized as part of the main study, and not separately randomized.

At randomization, 5 subjects age 65 to 74 years of age will be recruited as a sentinel group to confirm the safety of the older age group. When the sentinel group is vaccinated with the clinical trial drug, the vaccination is carried out at an interval of at least 24 hours between each subject. Once five subjects aged 65 to 74 years have been enrolled into the sentinel group, if no adverse drug reactions that meet study criteria for stopping vaccination of a clinical investigational drug have not been observed, then registration of the remaining older age cohort subjects can proceed.

Exploratory goals of the Phase I study will examine (1) the effect of a single vaccination to induce IgG antibodies, and (2) whether passive transfer of immune serum from vaccinated study participants will protect against disease in an animal challenge model of SARS-CoV-2 infection. Exploratory goals of the Phase II study will examine whether (1) SARS-CoV-2 seropositive individuals at baseline experience boosting of their immune responses with vaccination and will also explore (2) the durability of vaccine induced immune responses through the assessments at long-term follow up visits, (3) immune responses differ for those who are age 66 to 85 years older relative to those age 65 and younger.

Serologic immune responses will be determined by ELISA testing with the SARS-CoV-2 spike (S) and ORF3a proteins as antigen targets. T cell responses will be determined by ELISPOT assays using overlapping 15-mer peptides spanning the entirety of the S and ORF3a proteins. Neutralizing antibody responses will be determined either by live virus, pseudovirion, or binding inhibition assay(s).



[CoV2-001 clinical trials scheme]

A summary of the vaccination evaluation is presented in Tables S2, S3 and S4.

Safety assessment: All subjects will be monitored for

- Local and systemic adverse events at each study visit.
- Laboratory-related adverse events after each vaccination.

Immune Response Assessment:

The test will assess cellular and humoral immune responses in blood samples collected after baseline and vaccination according to Table S2.

The duration of this clinical trial is as follows.

About 20 months from the date of approval of the clinical study by the Ministry of Food and Drug Safety and the Institutional Review Board

- Recruitment period for test subjects: about 5 months
- Clinical trial period for each subject: at least 48 weeks

3.1 Interim Safety Monitoring

As part of the Phase I study, two interim safety reviews will be performed. A review of AE's and laboratory results will occur after all subjects in Study Arm 1a (0.6 mg) have received their 1st dose of vaccination and have completed the Week 1 safety visit. A formal Interim Analysis will be performed after study visit 4, four weeks after the 2nd vaccination to review AE's and binding antibody responses to select the vaccination regimen to be used for the Phase II study.

Subject diaries to be reviewed at the next visit after vaccination are distributed to the subjects, and symptoms of local and systemic reactions are collected and documented 7 days after vaccination.

As part of the Phase IIa study, an interim safety review will be performed after all participants have completed through the 4th study visit corresponding to the post-immunization visit after the primary vaccination series. Safety and immunogenicity will be determined and compared between groups as well as for the subgroup who are age 66 to 85.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment of Participants

Healthy adult volunteers will be recruited for the study.

4.2 Inclusion Criteria

1. Age greater than 19 to 85 years of age (Phase I will be restricted to an upper age limit of 50 years of age); Phase IIa will allow enrollment of 30 persons 66 to 85 years of age.
2. Able to provide informed consent

3. Able and willing to comply with study procedures
4. For women of child-bearing potential, able and willing to utilize an approved form of pregnancy prevention through to 4 weeks post-boost vaccination.

   Approved forms of pregnancy prevention are as follows,

   ① Hormonal contraceptives (e.g., oral progesterone single or estrogen-progesterone complex, transdermal delivery type contraceptives, depot injections, etc.)

   ② Implantation of intrauterine devices or intrauterine systems

   ③ Double blocking method [male physical blocking method (eg. male condom) and female physical blocking method (eg. cervix cap, contraceptive diaphragm, contraceptive sponge] are used in combination, and spermicide is used together. The use of condoms in all cases is not recommended as damage from physical friction may be less effective than expected contraception.)

   ④ Surgery and operation status such as tubal ligation (resection), hysterectomy, and vasectomy (resection)

4.3 Exclusion Criteria

1. Current or planned pregnancy through to 4 weeks post-boost vaccination for women of childbearing potential
2. Currently breastfeeding
3. Current or past participation in a coronavirus (MERS-CoV, SARS-CoV-2) vaccine study
4. Administration of an investigational agent within 6 months of the 1st dose
5. Administration of a vaccine within 28 days prior to the 1st dose
6. Administration of immune globulin or blood-derived medicinal product within 16 weeks of enrollment
7. Administration of an anti-TNFα inhibitor such as infliximab, adalimumab, etanercept, or rituxumab within 24 weeks from enrollment
8. Current daily treatment of systemic corticosteroids of 20 mg of prednisone or greater, dexamethasone of 3 mg or greater, or equivalent dose of other systemic corticosteroids
9. Administration of any Immunosuppressive Drug or Immunomodulator within 3 months of the 1st dose
10. History of bone marrow transplantation
11. Current or planned chemotherapy treatment for hematologic or solid tumor during study period or treatment during the 5 years prior to enrollment
12. Respiratory disease (ex. Asthma, Chronic obstructive lung disease) that is uncontrolled per their treating physician
13. Cardiovascular disease (ex. myocardial ischemia, congestive heart failure, cardiomyopathy, clinically significant arrhythmia) that is uncontrolled per their treating physician
14. Uncontrolled Hypertension (Systolic pressure >150mmHg or Diastolic pressure >95mmHg)
15. Uncontrolled Diabetes
16. Severe allergic reaction or anaphylactic reaction after vaccination in the past

17. Immunosuppresion including immunodeficiency disease or family history
18. Positive of serum test at screening of Hepatitis B surface antigen, Hepatitis A IgM, HIV, or Hepatitis C. Those who are Hepatitis C seropositive are allowed to participate if thtey have a negative HCV RNA test.
19. Baseline screening lab(s) with Clinically Significant abnormality (Grade 2 or higher)
20. Serious adverse reaction to a drug containing Investigational Product (GLS-5310) or other ingredients of the same categories or to a vaccine or antibiotic, nonsteroidal anti-inflammatory disease control, etc. or an allergic history
21. History of hypersensitivity to vaccination such as Guillain-Barre syndrome
22. History of PCR-confirmed infection with SARS-CoV-2 or positive SARS-CoV-2 antibody or PCR test at screening
23. Subjects who have been contact with COVID-19 infections in the past prior to administration, have been classified as COVID-19 confirmed patients, medical patients or patients with symptoms or have been identified with SARS and MERS infection history in the past
24. Acute over 37.5℃ fever, cough, difficulty breathing, chills, muscle aches, headache, sore throat, loss of smell, or loss of taste within 72 hours prior to administration
25. Healthcare workers participating in the medical examination of patients infected with COVID-19 or high-risk individuals who are likely to be occupationally exposed to SARS-CoV-2
26. Not willing to allow storage and future use of samples for SARS-CoV-2 related research
27. Prisoner or subjects who are compulsorily detained for treatment of a psychiatric illness
28. Any illness or condition that, in the opinion of the investigator, may affect the safety of the subject or the evaluation of a study endpoint
29. Receipt of a vaccine to prevent COVID-19 infection

4.4 Discontinuation/Withdrawal of Study Participants

Participants will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits. If a participant discontinues the study at any time after enrollment, but prior to the final scheduled study visit, the investigator will make every effort to have the participant complete all assessments. At a minimum, study participants will be encouraged to complete all procedures included in the final study visit should they elect to terminate early. All data collected up to the time of early termination will be used for final analyses except as noted below. Categories of early study termination are defined below:

- Voluntary withdrawal from the study: the participant verbalizes or states in writing their desire to withdraw from the study. Data already collected remains as part of the study.
- Dropout : the participant has a potentially life-threatening adverse event, grade 4 adverse event, or death that is judged to be related to the vaccination of the investigational product, or anaphylaxis of grade 3 or higher that is considered to be related to the vaccination of the investigational product is reported.
- Withdrawal of consent: When the subject makes a verbal or written request to cease participation in the clinical trial and also withdraws consent to the use of all clinical trial data. If the subject agrees to the use of clinical trial data already collected after discussion

with the investigator, the subject is classified as “Stop participating in voluntary clinical trials”.

- Lost to follow-up: the participant terminates, does/will not return to complete study visits and cannot be located, or does not respond to multiple attempts at contact.
- Major protocol violation: the participant failed to adhere to protocol requirements. Such events will be discussed on a case-by-case basis between the Medical Monitor and the site Principal Investigator (PI) to determine whether these events constitute a deviation that requires removal of the participant from the study and/or non-use of study data.
- Adverse event (Adverse Drug Reaction): clinical or laboratory events that in the medical judgement of the investigator are grounds for discontinuation for the best interest of the participant. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death: the participant died.

4.5 Clinical trial termination and early termination

In this clinical trial, the termination of the clinical trial of the last participant is defined as the termination of the entire clinical trial.

Meanwhile, the sponsor may early terminate the clinical trial site or the clinical trial at a specific clinical site (discontinue or stop of the clinical trial). The reasons for early termination of the clinical trial by the sponsor include, but are not limited to:

1) In case of failure to register the target number of participants in all or a specific clinical site

2) In case of occurrence of efficacy/safety information that may have a significant impact on the continuation of the clinical trial

① In case of serious adverse event or grade 4 or higher adverse event related to vaccination of investigational product

② In the case of more than 20% of the participants who occurred grade 3 or higher adverse events continuing for one or more days in each cohort

3) If there is a violation of good clinical practice (GCP), clinical trial protocol or contract by the clinical trial site or investigator that interferes with continuation of the clinical trial

4) Other administrative reasons that may have a significant impact on the continuation of the clinical trial

Investigator and Institutional Review Board may be terminated in early stage according to the information collected or observed during the clinical trial if it is judged that the benefits that can be obtained by individuals and society do not exceed the risks and inconveniences or cannot justify them.

In the case of early termination of the clinical trial, the following is required.

1) If the investigator terminates the clinical trial prematurely without prior agreement with the sponsor, the investigator immediately informs the sponsor and the IRB of this fact and submits a detailed reason for early termination and suspension.

2) If the sponsor terminates or early terminates the clinical trial, the investigator immediately informs the IRB of this fact and submits a detailed reason for the early termination or suspension.

3) If the IRB early terminates or suspends the clinical trial, the investigator immediately informs the sponsor of this fact and submits a detailed reason for the early termination and suspension.

4) In case the relevant clinical trial is prematurely terminated or suspended according to the provisions of 1) to 3), the investigator immediately informs the subject of this fact so that appropriate measures and follow-up can be made.

5. STUDY PROCEDURES AND ADMINISTRATION PLAN

5.1 Overall Procedure

This Phase I / II study will assess the safety, tolerability, and immunogenicity of GLS-5310 DNA vaccine.

The Phase I portion of this study is an open-label, dose escalation study to assess two dose levels of GLS-5310 DNA vaccine (0.6 and 1.2 mg) as part of two vaccination regimens (0-8 weeks and 0-12 weeks). After enrolling study arm 1a (0.6 mg), participants will be randomized to study arms 1b and 1c. GLS-5310 will be administered via intradermal (ID) injection using the Mantoux technique followed by suction applied over the vaccination site using the JM-11 device. The primary outcome measures are (1) the safety and tolerability of GLS-5310 given ID with JM-11 and (2) binding antibody responses elicited by vaccination. Secondary outcome measures are the (3) T cell responses elicited to vaccine antigens and (4) neutralizing antibody titers. Exploratory goals of the study are to determine the IgG antibody responses after a single vaccination relative to treatment arm and whether passive transfer of immune serum can protect animals from pulmonary disease.

Dose escalation within the Phase I portion of the study will occur as follows. Study arm 1a (0.6 mg per vaccination) will be vaccinated and followed to the Week 1safety visit. If no vaccine-associated severe adverse events (SAEs) have been documented, then enrollment into study arms 1b and 1c (1.2 mg per vaccination) will occur in a randomized manner. Phase I subjects complete Visit 4, an interim analysis to evaluate safety and binding antibody response is performed. The assessment of adverse events is performed after visit 1 to study arm 1a. The interim analysis are performed after visit 4 for study arms 1a, 1b, and 1c of the Phase I, and after visit 4 for study arms 2a and 2b of the Phase IIa. In order to advance to Phase IIa, the seroconversion rate for the antibody binding between the study arms is >70%, and the incidence of serious adverse reactions (Grade 3 or higher) related to the investigational drug should be no more than 1 case. In addition, the safety and immunogenicity results are evaluated on the data and safety monitoring board (DSMB). Escalation to Phase IIa will occur based on the interim analysis.

The Phase IIa portion of this study is designed as a randomized, double-blind, placebo-controlled study with only a single active study drug arm. Subjects will be randomized to receive either

placebo or GLS-5310 vaccine in a 1:2 ratio. Included are those who are 66 to 85 years of age (restricted to 30 persons total) and meet inclusion and exclusion criteria as specified. The latter will not be separated from the overall randomization schema.

5.2 Administration of GLS-5310 vaccine

ID vaccine administration with JM-11 is performed by first administering vaccine (0.1 mL) intradermally via Mantoux injection with a 1 mL tuberculin syringe with a 25 or 26 gauge needle (Figure 5.2-A) that generates a bleb or "bubble" in the skin. It is important that the needle angle be very shallow as shown in the photo. After injection, a clean tip is applied on the JM-11 device, the opening of the tip of the JM-11 device (Figure 5.2-1b) is applied over the bleb, encircling as much of the bleb as possible. The JM-11 device is then turned ON by pressing the button and held in place while suction is applied. The JM-11 device will turn off automatically after 30 seconds. After use, the tip is discarded, the device cleaned with an alcohol wipe, and then placed into a plastic bag and labelled with the participant's name. For this study, devices will *NOT* be shared between participants.

Figure 5.2-1 A) Example of ID Mantoux injection and B) JM-11device.

Following vaccine administration, the participant will be asked to assign a VAS score for the administration event itself and again at 15-20 min.

5.3 Concomitant Treatment

5.3.1 Allowed Concomitant Treatment

Except for Prohibited Concomitant Treatment (Section 5.3.2), other than investigational products (drugs and non-drugs) can be used at the discretion of the investigator if medically necessary.

5.3.2 Prohibited Concomitant Treatment

The following concomitant treatment affecting/expecting to affect the efficacy and safety evaluation of the investigational product should be prohibited during the 4 weeks after the last vaccination, and some treatments from before participation in the clinical trial.

The drug treatment corresponding to the prohibited concomitant treatment is as follows.

- Other vaccines except investigational product (within 28 days before first administration of investigational product).

- Immunoglobulin or blood-derived drug (within 16 weeks before registration for clinical trial)

- Anti-TNFα inhibitors such as Infliximab, adalimumab, etanercept or anti-CD20 mAb (within 24 weeks prior to clinical trial registration)

- Prednisone 20 mg, dexamethasone 3 mg or more systemic corticosteroids or other systemic corticosteroids in equivalent doses (within 7 days before administration of clinical trial drug)

- Immunosuppressant or immunomodulator (within 3 months before administration of clinical trial drug)

-Chemotherapy

6. STUDY PRODUCT

6.1 Investigational Product

GLS-5310, the investigational vaccine used in this study, contains a DNA plasmid that encodes the SARS-CoV-2 spike (S) and ORF3a proteins and is formulated in SSC buffer. GLS-5310 will be supplied sterile, in clear glass vials with a recoverable volume of 0.3 mL.

The placebo used in the Phase IIa consists only of SSC buffer that does not contain the active ingredient, the plasmid, and is supplied in a clear glass vial with a practical amount of placebo of 0.3 mL.

Table 6.1-1 summarizes the ingredients and amounts of vaccines and placebo for clinical trials.

Table 6.1-1 Summarize the ingredients and amounts of vaccines and placebo

	Investigational Product	Placebo
Drug Substance (active ingredient)	pGO-1002 (SARS-CoV-2 Spike, ORF3a Protein expressed plasmid)	- (no active ingredient)
Diluent	Sterile saline sodium citrate (SSC) buffer	Sterile saline sodium citrate (SSC) buffer
Amount	1.8mg	- (no active ingredient)
Volume	0.3mL	0.3mL

6.2 Packaging and Labeling

Study product will be labelled as shown in Table 5.2-1.

Investigational products are labeled with whether the vial contains the GLS-5310 DNA vaccine or SSC placebo, as shown in Table 5.2-1.

Table 6.2-1. Study drug product labels (for Phase I)

Biologic Product/ Placebo	Sample Label
GLS-5310	GLS-5310 [6 mg/ml] 0.3 mL/Vial Single Use Vial Lot: GLS-5310.xxxxx Date of Manufacture: DD MMM YYYY Final Retest Date DD MMM YYYY Store at 2 - 8ºC CAUTION New Drug – Limited by Federal Law to Investigational Use GeneOne Life Science, Inc.
SSC	SSC 0.3 mL/Vial Single Use Vial Lot: xxxx.xxxxx Date of Manufacture: DD MMM YYYY Final Retest Date DD MMM YYYY Store at 2 - 8ºC CAUTION New Drug – Limited by Federal Law to Investigational Use GeneOne Life Science, Inc. Rev 000

For the Phase IIa portion of the study, the unblinded site pharmacist will dispense filled syringes to blinded study personnel that are labelled with only the subject ID# to maintain treatment blind.

6.3 Handling of Study Drug

Study drug will be stored at 2 - 8°C in a secure area according to local regulations. Refrigerators are required to have temperature monitoring and study staffs are required to maintain temperature monitoring logs.

6.4 Dispensing of Study Drug

It is the responsibility of the Investigators that study drug is dispensed only to study participants. Authorized personnel are the only ones to dispense product according to local regulation.

Study drug will be drawn up into syringes for ID injection. The syringes should be directly labelled with the participant identification number and date and time filled, and the syringes or cartridge put into a labelled envelope. Study drug should be administered within 6 hours from when study drug has been removed from the vial. The syringes are not to be labelled as to study drug.

6.5 Precautions with Investigational Medicinal Product

Investigational agent is to be administered only to participants who have completed informed consent for this clinical study.

6.6 Preparation of Investigational Product

Non-Luer lock TB tuberculin syringes will be loaded with 0.1 mL of GLS-5310 vaccine. For participants who are to receive vaccine at a 0.6 mg dose, a single tuberculin syringe will be filled with 0.1 mL of vaccine. For participants who are to receive vaccine at 1.2 mg dose, two tuberculin syringes will be filled to 0.1 mL. The syringes should be labelled with the participant ID#, date, and time filled.

6.7 Record of Investigational Product Disposition at Site

Investigators should maintain and manage the latest records of storage, distribution/return/disposal of investigational drugs at each site. Records and logs must comply with applicable regulations and guidelines and include the following:

• Quantity in storage at the designated place after receipt

• Quantity currently stored in the designated location

• Label identification number or batch number and expiration date

• Initials and dates of the person in charge of inventory/delivery of each investigational drug

• Quantity issued to each subject, including a unique subject identification number.

• Quantity transferred to another location/site for delivery or storage

• If applicable, the quantity discarded by the laboratory.

6.8 Return and Destruction of Investigational Product

Once monitoring of Investigational Products is completed by GeneOne or its designee, pharmacy will destroy any remaining investigational product. Pharmacy will document destruction of used and/or unused vials on the pharmacy logs.

6.9 Use of JM-11

JM-11 is a cosmetology device or an equivalent or higher device to apply mild suction.

There is no need to receive specialized training because JM-11 is brought into contact with the bleb formed after intradermal administration of GLS-5310. The operation of the device is in accordance with Section 5.2.

6.9.1 Purpose of use and principle of operation

When GLS-5310 is administered intradermally and aspirated by touching the disposable sterile tip of JM-11 to the blister formed after intradermal administration, physical stimulation is delivered

to the intradermal cells of the injection site, thereby enhancing the vaccine immune response. The physical stimulation caused by this suction is composed of a slight shear force and a compressive force that adsorbs the skin, so there is no safety concern such as skin damage.

6.9.2 Information of JM-11

-

-Product # : JM-11

-Manufacturer : Qubist

-Suction pressure and operation time : 65kPa, 30 sec

-Device

- Disposable sterile suction tip

6.9.3 Education and qualification

Intradermal administration and suction procedures do not require qualifications, but the sponsor conducts training to the investigators in advance.

6.10 Device Accountability

Sites will document the number of each type of device received and lot number. Each participant will be assigned a JM-11device, such that devices are not to be used on multiple participants. After the 1st vaccination, the sponge protector is removed and the sponge replaced, the tip is removed and discarded, the device cleaned with an alcohol wipe, and the device placed into a plastic bag and labelled with the name of the participant. The same device is to be used for the 2nd vaccination with a new tip applied, after which processing is the same. GeneOne will instruct the site in the disposition of the devices after the study.

7. STUDY PROCEDURES AND TREATMENTS

7.1 Procedures by Visit (also see Tables S2 and S3)

7.1.1 Visit 1: Determine eligibility, obtain informed consent, enrollment, 1st vaccination

Prospective study participants will be assigned a unique participant identification number (PID#), and then interviewed to determine study eligibility.

Those who meet study criteria will complete an informed consent and be enrolled into the study to complete the following procedures:

- Review and record medical history (last 24 weeks)
- Review and record participant demographics
- Review and record prior and concomitant medications in past 24 weeks
- Perform and record physical examination and vital signs
- Record height and weight
- Collect blood for hematology and chemistry safety labs (baseline values)
- Collect blood for serological testing (Hepatitis B, Hepatitis A, HIV, Hepatitis C)
- Chest X-ray test
- 12-Lead ECG test
- PCR or Antibody screening test (SARS-CoV-2)
- Record most recent HgbA1c (diabetics only)
- Collect blood for immunology testing (serum and PBMCs baseline values)
- Collect urine for pregnancy testing (women of childbearing potential)
- Administer study drug (GLS-5310 or placebo depending on randomization results)
- Perform VAS score and record
- Distribution of subject diary after vaccination
- Check whether or not immediate adverse events (anaphylaxis-related) occur within 30 minutes after vaccination of the investigational drug (in case of the elderly over 75 years of age in Phase 2a, immediate adverse events are observed until at least 2 hours after vaccination of the investigational drug)

7.1.2 Visit 2: Safety follow-up.

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events

- Review and record injection site reactions
- Review of subject diary
- Collect blood for hematology and chemistry

7.1.3 Visit 3: Follow-up and booster vaccination

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)
- Collect urine for pregnancy testing (women of childbearing potential)
- Administer study drug (GLS-5310 or placebo depending on randomization results)
- Perform VAS score and record
- Distribution of subject diary after vaccination
- Check whether or not immediate adverse events (anaphylaxis-related) occur within 30 minutes after vaccination of the investigational drug (in case of the elderly over 75 years of age in Phase 2a, immediate adverse events are observed until at least 2 hours after vaccination of the investigational drug)

7.1.4 Telephone Visit 1: Safety follow-up.

Study procedures to be completed include:

- Review and record adverse events
- Review and record injection site reactions

7.1.5 Visit 4: Post-vaccination follow-up, unblinding

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events
- Review and record injection site reactions
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)
- Inform participant of their treatment assignment
    - For those who received placebo, ask whether they would like to start vaccination series with GLS-5310(Refer to Section 7.2)

7.1.6 Visits 5, 6, 7: Follow-up

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Record vital signs
- Review and record adverse events
- Collect blood for immunology testing (serum and PBMCs)

7.1.10 Visit 8: End of Study or Early Termination (see above for Phase I)

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Record vital signs
- Review and record adverse events
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)

7.1.11 Unscheduled visits

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events

7.2 Procedures by Visit (GLS-5310 revaccination group, see clinical trial schedule S4)

7.2.1 Visit 1: Vaccination

- Review and record prior and concomitant medications
- Perform and record physical examination and vital signs
- Collect blood for hematology and chemistry safety labs (baseline values)
- Collect blood for immunology testing (serum and PBMCs baseline values)
- Collect urine for pregnancy testing (women of childbearing potential)
- Administer study drug (GLS-5310)
- Perform VAS score and record
- Distribution of subject diary after vaccination
- Check whether or not immediate adverse events (anaphylaxis-related) occur within 30 minutes after vaccination of the investigational drug (in case of the elderly over 75 years of age in Phase 2a, immediate adverse events are observed until at least 2 hours after vaccination of the investigational drug)

7.2.2 Visit 2: Safety follow-up.

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events
- Review and record injection site reactions
- Review of subject diary
- Collect blood for hematology and chemistry

7.2.3 Visit 3: Follow-up and booster vaccination

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)
- Collect urine for pregnancy testing (women of childbearing potential)
- Administer study drug (GLS-5310)
- Perform VAS score and record
- Distribution of subject diary after vaccination
- Check whether or not immediate adverse events (anaphylaxis-related) occur within 30 minutes after vaccination of the investigational drug (in case of the elderly over 75 years of age in Phase 2a, immediate adverse events are observed until at least 2 hours after vaccination of the investigational drug)

7.2.4 Telephone Visit 1: Safety follow-up.

Study procedures to be completed include:

- Review and record adverse events
- Review and record injection site reactions

7.2.5 Visit 4: Post-vaccination follow-up

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events
- Review and record injection site reactions
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)
- Inform participant of their treatment assignment

7.2.6 Visits 5, 6, 7: Follow-up

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Record vital signs
- Review and record adverse events
- Collect blood for immunology testing (serum and PBMCs)

7.2.10 Visit 8: End of Study or Early Termination

Study procedures to be completed include:

- Review and record concomitant medications

- Perform targeted physical exam (relevant to participant system-specific complaints)
- Record vital signs
- Review and record adverse events
- Collect blood for hematology and chemistry
- Collect blood for immunology testing (serum and PBMCs)

7.2.11 Unscheduled visits

Study procedures to be completed include:

- Review and record concomitant medications
- Perform targeted physical exam (relevant to participant system-specific complaints)
- Perform and record vital signs
- Review and record adverse events

7.3 Timing and Evaluations

7.3.1 Informed Consent

Study personnel will meet with prospective study participants, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, study treatments and follow-up procedures. An informed consent must be signed prior to any study related procedures being performed. A copy of the signed and dated consent form will be given to the participant.

7.3.2 Enrollment and Intake visit

Participants who consent to be in the study will be assigned a unique PID#. Once assigned, PID#s cannot be reused for any reason. Information regarding participant's PID# and screen date will also be documented on a screening log.

Medical History

Investigators should document all significant illnesses that the participant has experienced as Medical History within the past 24 weeks. Illnesses' first occurring or detected during the study and/or worsening of an existing illness that occurs after the first administration of study drug are documented as AEs on the electronic case report form (eCRF).

Prior / Concomitant medications

Prior treatments for a period of 24 weeks prior to enrollment will be recorded. Concomitant treatments, defined as continuing or new treatments taken at or after the signing of the informed consent, will be recorded in the eCRF as concomitant medications.

7.3.3 Adverse effects

Adverse effects that will be queried at each study visit include those related to the underlying disease and treatment, those potentially related to study drug, and those potentially related to study drug administration. AEs should be graded according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials" issued in September 2007 by the US FDA (Appendix A). Subjects record the response (local and systemic) after vaccination on the evening of each vaccination day and 7 days after each vaccination day in the subject diary (Appendix B).

Subjects record the response to the injection site using the measurement tool provided, and the investigator reviews the subject diary. The response results described are evaluated for clinical significance and recorded as appropriate in the CRF.

Subjects who develop Grade 1 or higher eosinophilia (eosinophil count of ≥ 650 cells/mm^3) will be asked to return weekly for repeat CBC determinations until resolution of the eosinophilia.

7.3.4 Weight and Height

Participant height and weight will be assessed and recorded at enrollment. BMI will be calculated automatically and recorded.

7.3.5 Chest X-ray test

At the screening visit, a chest X-ray is performed on all subjects to determine suitability for the subject's safety.

7.3.6 12-Lead ECG

An ECG will be performed at screening for all subjects to determine eligibility. The ECG should include measurements of ventricular rate, PR, QRS, QT, QT_cF with assessment as to whether the ECG is normal or abnormal. Abnormal ECGs will be interpreted as clinically significant or not clinically significant. Dosing will be delayed in the event of a clinically significant abnormal pre-dose ECG until it has been reviewed by the PI, qualified PI designee, Medical Monitor or Sponsor consultant cardiologist and deemed safe to proceed. The ECG should be labeled as either "normal", "not clinically significant", avoiding abbreviations such as NCS, or "clinically significant, but stable to proceed" and kept with source documentation; alternatively case notes can reflect the ECG reading as source documentation. The method of QT_cF determination should also be recorded and will be collected as part of the Case Report Forms.

7.3.7 PCR or Antibody test (SARS-CoV-2)

At the screening visit, a point of care PCR or antibody test is performed on all subjects to determine serologic evidence of prior SARS-CoV-2 infection.

7.4 Assessment of injection site

The injection site will be assessed by study personnel at each visit. Participants are to be instructed to monitor the site for signs of inflammation, redness, swelling, or pain and report these issues at the next study visit. Site staff will discuss any symptoms and determine whether these constitute AEs and record as appropriate. The subject should be instructed to record the exact symptoms, the diameter of the redness (cm), the diameter of the edema (cm), the diameter of the bruise (cm), and the date of onset and disappearance.

7.5 Immunogenicity assessments

Blood to obtain serum and PBMCs for immunogenicity assessments will be collected at all visits, except for Visit 2 and unscheduled visits. Serum will be evaluated for antibody responses by ELISA against the SARS-CoV-2 S and ORF3a proteins. Serum will also be evaluated for neutralizing antibody responses. Induction of T cells will be determined by ELISPOT to determine interferon gamma (IFN-γ) responses of PBMCs against pools of 15-mer peptides spanning each target antigen.

8 Safety assessments

8.1.1 Safety Parameters

1) Adverse events

2) Vital signs

3) Laboratory evaluations

4) Injection site reaction evaluations

8.1.2 Safety Evaluations

8.1.2.1 Adverse Events (AEs)

8.2.1.1 Definition of Adverse Events

An AE (also referred to as an adverse experience) is defined as any unfavorable and unintended sign, symptom or laboratory abnormality that is temporarily associated with the use of a drug or treatment and does not imply any judgement about causality. An adverse event can arise with any use of a drug or treatment regardless of route of administration, dose, and may be delayed after a drug or treatment has been discontinued. An adverse event is not the same as an "overdose"; an overdose is a dose-related event specifically caused by exposure to an increased amount of drug.

Adverse drug reactions (ADRs) are all adverse and unintended reactions that occur at any dose of a study drug, and the causal relationship with the study drug cannot be denied.

Adverse events of Special Interest (AESI) include enhanced disease of the immune system, and the following symptoms can be monitored more closely:

• Patient with documented vital signs with: respiratory rate of ≥30 breaths per minute, heart rate ≥ 125 per minute, SpO2 of ≤ 93% on room air, or PaO2/FiO2 of < 300 mm Hg.

• Respiratory failure (requirement for high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO)

• Shock (systolic BP of <9 0 mm Hg, or diastolic BP < 60 mm Hg, or need for vasopressors)

• Significant acute renal failure, hepatic or neurologic dysfunction

• Admission to ICU

• Death

An unexpected AE is:

- Not identified in the IB or otherwise not expected from the characteristics of the clinical material
- Not listed at the specificity or severity that has been previously observed

Treatment emergent AEs (TEAE) include the following:

- Post-treatment complications that occur as a result of protocol mandated procedure
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug, will also be considered an AE
- Complications and termination of pregnancy; see Section 7.1.8 for additional information.
-

Study related AEs do not include the following:

- Elective medical or surgical procedures
- Non-elective medical or surgical procedures (Medical or surgical procedure (e.g. surgery, endoscopy, extraction, blood transfusion); On the other hand, the conditions that led to these procedures are considered adverse events.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before study enrollment or prior to the first administration of study drug and dose not worsen
- Conditions where no undesirable medical event has occurred (e.g. hospitalization for planned surgery, hospitalization for social and/or accommodation)
- Incorrect or increased dose administration of study drug without adverse clinical sequelae
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before study enrollment or prior to the first administration of study drug and dose not worsen. It is considered pre-existing and is recorded as a medical history in the eCRF.

- Any laboratory abnormality that is considered as non-significant
- Uncomplicated pregnancy
- An induced termination of pregnancy without medical reason

8.1.2.1.2 Serious Adverse Events (SAEs)

A SAE is any AE that meets one of the following conditions

- Death
- Life-threatening event.
- Event that requires inpatient admission to a hospital; (If hospitalization or extension of the existing hospital stay is required during the observation period defined in the clinical trial protocol (even if the hospitalization is made as a preventive measure for continuous observation, one night at the hospital regardless of the length of stay) This includes the case of doing things).

Note: Observation, non-hospital evaluation, in a physician's office, hospital, or other emergency care setting, regardless of the duration of observation, is not a SAE;)

- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity;

Is an important medical event that may not result in death or be life threatening, but based upon appropriate medical judgment, may jeopardize the participant and may require medical or

surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm and newly occurred convulsions.

8.1.2.1.3 Solicited local/systemic AE

In the vaccination of this investigational drug, a feeling of pulling the skin may occur due to suction, and potential adverse events of the investigational drug may include erythema, pain, heat, or partial swelling at the injection site. Other adverse events that occur are included in the unexpected adverse events.

The solicited local and systemic adverse events can be summarized as follows.

Table 8.1.2.1.3-1 Solicited local/systemic AE

Common	• Mild to moderate administration site pain, erythema, tenderness, swelling, induration • Malaise/fatigue, myalgia, or headache in the first few days following injection • Visible lesion(s) at the injection site, such as erythematous papules with eschar, hypopigmentation, hyperpigmentation
Less common	• Administration site bruising/ecchymosis, hematoma or pruritus • Arthralgia or nausea • Injection site hematoma, bruising/ecchymosis, laceration, other transient lesions, or bleeding related to the injection procedure • Eosinophilia
Uncommon or rare	• Administration site, laceration, other transient lesions, or bleeding related to the injection procedure • Severe administration site pain or tenderness • Rash following injection/EP • Keloid scar or hypertrophic scar formation • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Muscle damage at the administration site • Autoimmune disease • Effects on the fetus and on pregnancy

8.1.2.1.4 Unexpected Adverse Drug Reactions (ADRs)

Unexpected ADR refers to an adverse drug reaction that differs in its pattern or severity of harm compared to the information of the investigational drug (refer to the investigator's data sheet). This includes delayed events such as anaphylaxis or allergic reactions related to vaccine administration, and unexplained neurological events.

8.1.2.1.5 Evaluation of adverse events

All items identified for the adverse reaction, such as occurrence, symptom, date of onset, date of disappearance, severity, relationship with the investigational drug, related measures, treatment, and results, should be recorded in the e-CRF.

Abnormal values of laboratory tests that are considered clinically significant, vital signs, and abnormal findings of ECG results are recorded as adverse reactions.

8.1.2.1.6 Assessing Severity (Intensity)

The Investigator will grade laboratory AEs and clinical AEs (based on discussions with study participants) using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix A):
Adverse events will be recorded on the eCRF at the severity reported by the Investigator.

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)

8.1.2.1.7 Causal Relationship of Clinical Material to Adverse Events

A causally related AE is one judged to have a suspected relationship to the administration of the investigational agent. Conversely, an AE may also be assessed as not related to the investigational product. The Investigator is responsible for reporting adverse events and judging the relationship between the administration of the investigational product and an AE because the investigator is knowledgeable about the participant (e.g., medical history, concomitant medications), administers the investigational product, and monitors the participant's response to the investigational product. The Sponsor will assess the overall safety of the investigational product and determine whether expedited reporting to regulatory agencies is indicated.

Investigators should use their knowledge of the Study Participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug by the following criteria:

- Related – the Investigator considers that there is a causal relationship between the event and study drug;
- Probably related – the Investigator considers that there is a probability of a causal relationship of the event to the study drug
- Possibly related – the Investigator considers that there is a possible causal relationship of the event to the study drug
- Not related – the Investigator considers that the event has no relationship to administration of the study drug

The following guidance should also be taken into consideration:

- Temporal relationship of event to initiation of study drug;
- Course of the event, discontinuation of study drug, or reintroduction of study drug (when applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study (as applicable);

- Presence of risk factors in the Study Participant or use of concomitant medications known to increase the occurrence of the event

8.1.2.1.8 Measures related to investigational products

Any of the following measures with regard to investigational product dosing during the study if adverse events, abnormal laboratory values occur or in response to immunologic assessments:

1) Maintain the study drug dose
2) Increase the study drug dose
3) Decrease the study drug dose
4) Cessation of administration of study drug
5) Not applicable

8.1.2.1.9 Treatment for adverse Events

Any of the following treatment measures that may be implemented during the study related to adverse events should be documented:

1) Treatment with medication therapies
2) Treatment with non-medication therapies
3) Treatment with both medication and non-medication therapies
4) No treatment

8.1.2.1.10Consequences of adverse Events

Any of the following consequences of abnormal events may occur and should be documented:

1) Recovered
2) Recovering
3) Not Recovered
4) Recovered, but after-effects remain
5) Death
6) Unknown

8.1.3 Physical Assessments and Targeted Physical Assessment

A complete physical examination will be performed at study enrollment. Targeted physical examinations based on symptoms will be performed at subsequent visits based on participant complaints.

8.1.4 Vital Signs

Participant vital signs will be performed and recorded at all study visits.

8.1.5 Safety Laboratory Evaluations

Blood for a complete blood count with differential(RBC, hemoglobin, hematocrit, platelet, WBC, neutrophil, lymphocyte, monocyte, eosinophil, basophil) and chemistries (consisting of sodium, potassium, blood urea nitrogen (BUN), creatinine, glucose, ALT, and bilirubin, Ca, Cl, AST, ALP, CPK, albumin, total protein, total cholesterol) will be performed at Visits 1, 2, 4 and 8. A urine pregnancy test will be performed at Visit 1 and Visit 3 for those of childbearing potential. Laboratory test abnormalities are generally not recorded as adverse events or serious adverse

events. According to the judgment of the investigator, a clinically significant abnormal value is reported as an adverse event, and if it is related to a clinical adverse event, it is reported as the name of the adverse event. For laboratory test results, normal/abnormal evaluation is performed according to the normal range of the clinical trial site, and the severity is evaluated by the Toxicity Grading Scale.

8.1.6 Procedures for Documenting Pregnancy During Study

Women of childbearing potential who are pregnant or expect to become pregnant within 4 weeks from the boost vaccination, or who cannot agree to use an approved form of birth control will be excluded from participation in the study. Approved forms of pregnancy prevention are as follows,

① Hormonal contraceptives (e.g., oral progesterone single or estrogen-progesterone complex, transdermal delivery type contraceptives, depot injections, etc.)

② Implantation of intrauterine devices or intrauterine systems

③ Double blocking method [male physical blocking method (eg. male condom) and female physical blocking method (eg. cervix cap, contraceptive diaphragm, contraceptive sponge] are used in combination, and spermicide is used together. The use of condoms in all cases is not recommended as damage from physical friction may be less effective than expected contraception.)

④ Surgery and operation status such as tubal ligation (resection), hysterectomy, and vasectomy (resection)

Approved birth control methods include use of pills or injections of hormones to prevent pregnancy, use of a male or female condom with or without use of a spermicidal cream or gel, use of a diaphragm or cervical cap with concomitant use of a spermicidal cream or gel, IUD, or sexual abstinence. Should a participant become pregnant after enrolling in the study, she will not be given any further study treatment.

Participants who become pregnant at any point during the study will continue to be followed for clinical safety assessments without receiving further investigational product. The Investigator will report any pregnancies to the study team and medical monitor (or designee), and to the Investigational Review Board (IRB). Sites should request the participant's permission to follow the outcome of the pregnancy documenting such in the clinical study report.

Subjects whose pregnancy is confirmed during the clinical trial period are followed up for safety evaluation with the vaccination of the investigational product discontinued. The decision regarding collection of safety and/or immunology labs will be deferred to the PI.

If the participant does not wish to continue in the study and complete safety measurements, they will be listed as having withdrawn voluntarily.

8.1.7 Post-study Reporting Requirements

SAEs, including deaths, regardless of cause or relationship, must be reported to Sponsor at the time that such events become known to the Investigator.

Investigators are not obligated to actively seek AEs or SAEs beyond the follow up period for participants. However, if the Investigator learns of an SAE that occurs within 30 days from

completion or termination visit, the Investigator should promptly document and report the event to the study team and medical monitor.

8.2 Methods and Timing for Collection and Recording of Safety Data

At the time of each study visit, participants will be queried as to adverse events that have occurred in the interim period and the current status of any AE that was reported at a prior visit that has not yet resolved. Additionally, labs will be reviewed for safety.

All AEs, regardless of severity, seriousness, or presumed relationship to study treatment, must be recorded using medical terminology in source documents and on the eCRF. Whenever possible, a diagnosis will be documented, in lieu of symptoms. The source document and the eCRF must contain the Investigator's opinion concerning the relationship of the AE to study treatment.

AEs should be described with the following attributes:

- Duration (start and end dates)
- Seriousness
- Severity
- Causality
- Action(s) taken
- Outcome

8.3 Safety and Toxicity Management

The Medical Monitor will be responsible for the overall safety monitoring of the study. The site PI will be responsible locally for safety.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters
- Other clinically significant changes in safety evaluations

Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the participant's complaints will be documented.

8.3.1 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) are defined as any Adverse Events including:

- Grade 3 or greater systemic or local symptoms;
- Grade 3 or greater laboratory abnormalities
- Any episode of anaphylaxis or allergic reaction considered as study drug related or possibly study drug related

Sites will inform the Sponsor of any ERER within 24 hours, or increase of severity of an adverse event to Grade 3, to discuss whether dosing to the participant should continue.

8.3.2 Stopping Rules

If any of the following situations occur, then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and PI and the IRB (if applicable):

- Any participant experiences a potentially life-threatening AE, Grade 4 AE or death assessed as related to Study Treatment;
- Any report of anaphylaxis of Grade 3 or greater assessed as related to Study Treatment.

Any SAE or death assessed as related to Study Treatment will lead to an immediate halt of study enrollment and Study Treatments, until the event has been investigated.

8.3.3 Unblinding

The Phase IIa portion of the study will be unblinded at study visit 4 and subjects informed of their treatment status. Subjects assigned to the placebo group may elect to receive vaccine. Regardless of later vaccination status, all subjects will remain in study for safety evaluations.

In the Phase IIa study, all subjects, including those who were assigned to a placebo control group after unblinding, but subjects assigned to placebo who chose not to receive GLS-5310, will be followed for a year from study entry.

Treatment assignments through to the post-vaccination visit (Visit #4) should be maintained as blinded unless unblinding is considered critical to the care and well-being of the subject and that knowledge of the treatment assignment will affect medical management and medical decision making. Unblinding prior to visit #4 should occur following discussion with Sponsor Medical Monitor. However, emergency unblinding can occur if the Investigator deems that such a delay would unduly harm the subject and that knowledge of the treatment assignment is a critical factor in medical decision making versus discontinuation or temporary discontinuation of a study drug until discussion with the Medical Monitor. In the case of unblinding, the Investigator is not required to inform the Sponsor of treatment assignment. Unblinded treatment assignment should be made known only to those who require such information as part of medical decision making and for those involved in Safety reporting to Health Authorities and/or or the relevant IRB or local oversight body. In addition, the immunogenicity assay staff must remain blinded until the assay is complete.

Treatment assignments for immunologic measurement should be maintained as feasible throughout the study.

The Investigational Pharmacy at each site will maintain a listing of treatment assignments and will provide a mechanism for unblinding in emergency situations.

After unblinding, collect safety and efficacy results as much as possible even if you are not in the GLS-5310 vaccination group.

9. EVALUATION OF IMMUNE RESPONSES

9.1 Efficacy Parameters

1) Determine of GMT and seroconversion rate of SARS-CoV-2 Spike and ORF3a protein specific binding antibody responses induced by GLS-5310 relative to treatment arm(Endpoint titer of binding antibody in serum at each timepoint)

2) Determine of GMT and positive responder rate of the neutralizing antibody response induced by GLS-5310(plaque-reduction neutralizing titer in serum at each timepoint)
3) Determine the positive responder rate of T cell responses induced by GLS-5310(Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint)

9.2 Immunogenicity assessments

9.2.1 SARS-CoV-2 Binding ELISA

Standardized ELISA assays will be performed to measure the anti-SARS-CoV-2 S and ORF3a binding antibody responses. Samples will be scored as positive if the average optical density (OD) is greater than 0.10 absorbance units and greater than the average OD before immunization plus 2.5 times the standard deviation (SD) of the OD before immunization at the same dilution. Results will be presented as the geometric mean titer (GMT) of the antibody titer, end-point titer, i.e. the last dilution where the OD value is above the calculated threshold.

The definition of seroconversion as a positive response post-baseline at the lowest dilution tested (i.e. and antibody titer that is below 1:100 at baseline and after vaccination positive at or above the 1:100 dilution) assuming that the baseline response would be negative at 1:100. The criteria for the appropriate immunogenicity of the SARS-CoV-2 binding antibody is planned to have a positive response rate of 70% or more in each group at the interim analysis.

9.2.2 SARS-CoV-2 Serum Neutralization

Neutralizing antibodies against SARS-CoV-2 will be performed the geometric mean of the antibody titer (Geometric mean titer, GMT) to determine the 50% neutralizing titer (NT50) using a plaque-reduction neutralizing titer (PRNT) by standard methodology with relevant virus strains and cell lines. Alternately, pseudovirion-based neutralization assays and/or SARS-CoV-2 receptor binding inhibition assays may also be used to determine the breadth of the neutralizing antibody response to vaccination. The criteria for the appropriate immunogenicity of the SARS-CoV-2 neutralizinig antibody is planned to have a positive response rate of 70% or more in each group at the interim analysis.

9.2.3 SARS-CoV-2 ELISpot

Cellular immune responses will be assessed by measuring the number of SARS-CoV-2 antigen-specific IFN-γ secreting peripheral blood mononuclear cells (PBMCs) as determined by IFN-γ ELISpot assays. Cell responses to stimulation with SARS-CoV-2 peptides using 15-mer peptides overlapping by 10 amino acids spanning the entire S and ORF3a proteins will be measured and results reported as spot forming units per million cells (SFU/10^6 PBMC). Positive response cutoff calculations will include at least a fold-rise from subject-specific baseline SFU/10^6 PBMC values, based upon assay optimization criteria. The criteria for the appropriate immunogenicity of the SARS-CoV-2 T cell response is planned to have a positive response rate of 70% or more in each group at the interim analysis.

10. EVALUATION OF EXPLORATORY ENDPOINTS

10.1.1 Phase I Exploratory Endpoints

1) Determine binding antibody responses after a single dose of vaccine related to treatment arm (Endpoint titer of binding antibody in serum at each timepoint)
2) Determine whether passive transfer of human serum can protect against pulmonary infection from SARS-CoV-2 challenge in an animal infection model (Survival rate, blood and viral load

measurement of major organs, pathological examination of respiratory/lung area, immunogenicity evaluation)

10.1.2 Phase IIa Exploratory Endpoints

1) Determine the persistence of immune responses following vaccination with GLS-5310 (Endpoint titer of binding antibody in serum at each timepoint, Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint, plaque-reduction neutralizing titer in serum at each timepoint)
2) Determine the extent of immune boosting for participants who are seropositive at baseline following vaccination with GLS-5310 (Endpoint titer of binding antibody in serum at each timepoint, Antigen-specific interferon gamma (IFN-γ) secretion T-cell response in PBMC at each timepoint, plaque-reduction neutralizing titer in serum at each timepoint
3) Determine the relative immune responses for those who are age 65 years and younger versus those who are age 66 to 85 years

11. STATISTICAL METHODS and CONSIDERATIONS

Prior to analysis a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed.

11.1 Data Sets to be Analyzed

- The intention to treat population (ITT) includes all participants who sign informed consent.
- The modified intention to treat population (mITT) includes all participants who sign informed consent and who has received at least one administration of study drug. The mITT population will be the primary analysis population for outcomes.
- The safety set (SS) includes all participants who have received at least one dose of study medication. The SS will be the primary group for safety evaluations and outcome. Analysis of immune responses will be performed only for available samples.

Per-protocol (PP) analysis set includes all participants who complete the trial and who receive all vaccinations and have no significant protocol violations. Participants in this sample will be grouped to treatment arms they actually received. This set will be used as a sensitivity analysis to summarize the primary and secondary efficacy outcomes. For secondary and exploratory assessments of antibody and T cell immune responses, denominators will include only those participants who are SARS-CoV-2 seronegative at baseline. Unevaluable samples will not be considered as part of the denominator at relevant time points. For study participants who are seropositive at baseline, separate assessment of antibody and T cell responses will be performed.

The Phase IIa portion of the study will be unblinded at the post-vaccination visit (visit 4) and all persons who were randomized to the placebo arm offered vaccination with GLS-5310. Safety assessments will be determined based on the actual treatment received. Persons randomized to the placebo group who elect vaccination with GLS-5310 will then be considered to cross-over to the vaccination group as of Week 12. Persons randomized to the placebo group, and who decline vaccination will remain as part of the placebo group, regardless of whether such persons receive any other COVID-19 vaccine. Any study participant who receives an approved COVID-19 vaccine will remain as part of the group assignment as above.

11.2 Demographic and Other Baseline Characteristics

Demographic and baseline data, vital signs, medical history, concomitant illnesses, and current medications/treatments, including surgeries will be summarized by means of descriptive statistics: continuous variables as mean, median, standard deviation, and categorical variables as frequencies and percentages.

11.3 Safety Analysis

All safety and tolerability summaries will be performed on the SS.

11.3.1 Adverse events

Treatment emergent AEs will be summarized by frequencies and will be presented by system organ class and preferred term with the number and percentage of participants affected. Frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment.

Treatment emergent AEs will be summarized by estimates of proportions with exact 95% binomial CIs. The differences in proportion between the groups will also be calculated with 95% CIs. These frequencies will be summarized overall, by system organ class and by preferred term, for the number and percentage of participants affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. All serious AEs and administration site events will also be summarized as above.

The main summary of safety data will be based on events occurring within 28 days of administration of Study Treatment at the time of interim analysis; long term safety will be assessed through to 48 weeks following the final vaccination for each group.

VAS scores will be summarized with mean, median, minimum, and maximum values.

11.3.2 Laboratory Data

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values. Categorical response variables will be summarized per time point with percentages.

11.4 Immune Response Analysis

The study is not designed or powered to determine efficacy of the vaccine. However, immune response to the vaccine may be assessed by responder analysis of the immunogenicity data.

Immunogenicity results will be classified as responder/non-responder and will be analyzed as the frequency of responses for each assay for each treatment arm at each time point at which an assessment is performed. Estimates of proportions and exact 95% binomial CIs and 95% CIs for the differences between the groups will be calculated.

Immunogenicity analysis will be performed in the mITT and PP groups with evaluable immune response data.

11.5 Interim Analysis

An assessment of AE's will be performed after study visit 1 for Group 1a. For the Phase I study, an interim analysis will be performed after study visit 4. In order to enter Phase IIa, the seroconversion rate for the binding antibody reaction between test groups is evaluated on the basis of >70%. In addition, the incidence of serious adverse events (Grade 3 or higher) related to the investigational drug is evaluated as 1 or less. For the Phase IIa study, an interim analysis will be performed after study visit 4.

11.6 Sample Size and Randomization

This clinical trial is a phase 1/2a clinical trial to evaluate the safety and immunogenicity of GLS-5310 for the purpose of preventing COVID-19 set the required number of subjects.

For the phase 1 study, 45 subjects who meet the inclusion and exclusion criteria will be enrolled in order to secure 15 subjects to be vaccinated for investigational drugs for each vaccination group. For the phase 2a study, it was planned to secure 120 subjects based on randomization.

Randomization was performed 1:1 in groups 1b and 1c of the phase 1 study according to the pre-planned randomization generation number, and 2a, 2b in the phase 2a study to determine the difference between placebo and vaccine randomization is performed 1:2 in groups.

11.7 Missing Values

In the event that dates and/or times are missing for medications, medications will be assumed to be concomitant. In the event dates or times are missing for AEs, AEs will assume to be treatment emergent. Missing outcomes values, such as missed lab draws or invalid blood sample, missed vital signs, or missed or uninterpretable serum concentrations and PBMCs will be left as missing and not imputed. For the immunology analyses, statistical assessment will be based on available results.

In the event that a participant is enrolled in the trial but declines to be vaccinated then the site will enroll a replacement.

11.8 Unblinding

For safety analysis the study will be unblinded after database lock for analysis. Since subjects who were randomized to placebo will have the opportunity to be given the vaccine, safety assessments can be divided into 3 groups:

1) Randomized to vaccine
2) Randomized to placebo
3) Subset of Placebo subjects who received vaccine after unblinding

In addition, among the subjects assigned to the GLS-5310 vaccination group and the placebo group, the GLS-5310vaccinated group and the revaccinated group are analyzed separately.

12. DATA COLLECTION, MONITORING AND AE REPORTING

12.1 Confidentiality

Information about study participants will be kept confidential to the best of the study site's ability.

If a study participant cancels consent to the collection or use of personal health information (PHI), the sponsor may continue to use the information collected prior to the cancellation of the informed consent. For subjects who revoke consent to collection or use of PHI, consent should be obtained

for collection of critical conditions (i.e., survival of study participant), at least before completion of their planned clinical trial period.

12.2 Source Documents

Source data is all information, original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents and data records include (as applicable): hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, pharmacy records, laboratory records, medical records (including electronic records) relative to the clinical trial. For this study, documents relevant to documenting and verifying inclusion and exclusion criteria, prior medical history, concomitant medications, safety labs, and assessments relevant to any AE's are pertinent.

12.3 Data Collection

Data will be collected using Electronic Data Capture (EDC). Participants will be identified by PID#; no participant personal information (PPI) is collected as part of the EDC; nor is PPI retained as part of study data. All PPI is retained at each site and controlled by the site PI.

12.4 Record Retention

It is the Investigator's responsibility to retain study essential documents as per country regulations: in the US for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

12.5 Safety and Quality Monitoring and Record Availability

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor as outlined in the Monitoring Plan.

The investigator will make study documents (e.g., ICFs, drug accountability forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, regulatory agencies, GeneOne Life Science, Inc. or its designee for confirmation of the study data.

Participation as an Investigator in this study implies acceptance of potential inspection by regulatory authorities and applicable compliance and quality assurance offices.

12.6 Adverse event (AE) Reporting

AEs will be recorded and forwarded to regulatory agencies as required (e.g. Annual report).

12.6.1 Study Reporting Period of Adverse Events

All solicited and unsolicited adverse events are collected during the entire study period and recorded in the eCRF.

12.6.2 Study Reporting Period for Serious Adverse Events

SAE's will be recorded throughout the study and the 28-day follow-up period.

Expedited reporting of SAEs will be determined by GeneOne Life Science using reference safety information specified in the Investigator's Brochure. An event may qualify for expedited reporting to regulatory authorities if it is an SAE, SUSAR in line with relevant regulatory requirements.

At any time after completion of the SAE reporting period, if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to the study drug, the event will be reported to the Sponsor.

SAE TELEPHONE AND CONTACT INFORMATION:

SAE REPORTING	C&R Research	
		MAILING ADDRESS:
MEDICAL MONITOR:	Joel Maslow, MD PhD MBA	
PHONE:	(484) 965-9147p; (610) 331-7844 c	GeneOne Life Science, Inc.
	Hyojin Lee, M. Sc.	Parc.1 NH Finance Tower (Tower 2)
MEDICAL LIAISON:		20th floor, 108 Yeoui-Daero, Yeongdeungpo-Gu,
CELL:	02-3458-4058	
EMAIL:	hjlee@genels.com	Seoul 07335 Korea
GeneOne FACSIMILE:	02-3458-4042	
GeneOne Safety Email	hjlee@genels.com	

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Participant number and Study name
- Date of Onset and Date of Resolution (if applicable)
- Detailed description of event
- Investigational product (if known)
- Causal relationship of event to investigational product
- Reporter name and contact information

Follow-up reports will be sent as soon as more information becomes available. Events for which the study participant seeks medical care, the study site will attempt to obtain relevant medical records to include as source documents. These include but are not limited to discharge summary, results of relevant laboratory tests, and reports of relevant radiographic studies. In the case of death, the investigator will attempt to procure relevant reports (such as autopsy reports, medical examiner report, discharge summary).

Each SAE must be followed by the Investigator until resolution, stabilization, or return to baseline, even if this extends beyond the end of the study, with follow-up report filed to provide a summary of the event through resolution.

• The original SAE form must be kept at the study site. Copies (or electronic copy) will be provided to GeneOne Life Science or its representative, who will be responsible for reporting to regulatory authorities as indicated, and copy will be forwarded to the study sites IRB.

12.6.3 Notification of Serious Adverse Events

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected. Reports of SUSARs

shall be made as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Written notification may be submitted on the form described above or equivalent or in a narrative format and shall bear prominent identification of its contents. Each written notification to regulatory agencies shall be transmitted to the division that has responsibility for review. In each written safety report, the Sponsor shall identify all safety reports previously filed concerning a similar adverse experience and shall analyze the significance of the adverse experience in light of the previous, similar reports. The Sponsor shall also notify the relevant regulatory authorities by telephone or by facsimile transmission of all deaths regardless of causality and any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the Sponsor's initial receipt of the information. Each telephone call or facsimile transmission to regulatory agencies shall be transmitted to the division that has responsibility for review.

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a Sponsor's event investigation show that an adverse drug experience not initially determined to be reportable is, in fact, reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report. In the event of death, if an autopsy is performed, a copy of the report, redacted for PHI but labeled with the PID#, should be sent to GeneOne Life Science, Inc.

The MFDS may request the sponsor to submit the sponsor's monitoring report to the laboratory for the first case reported as "SUSAR causing death".

Through this, a survey can be conducted when necessary, such as finding that the investigator does not comply with major clinical trial standards.

12.7 Study Discontinuation

GeneOne Life Science reserves the right to discontinue the study for safety or administrative reasons, including lack of enrollment, at any time. Investigational product must be returned to GeneOne, unless instructed otherwise. Document retention will follow local regulation.

13. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 Clinical trial management standards and Declaration of Helsinki

The procedures specified in this protocol are the international council for harmonization of technical requirements for pharmaceuticals for human use-good clinical practice (ICH-GCP), Korean good clinical practice (KGCP) and Declaration of Helsinki.

This clinical trial will be conducted in accordance with the ethics regulations based on the Declaration of Helsinki, ICH-GCP, KGCP and related laws.

13.2 Consent of Study Participant

1) The investigator must give the study participant (the study participant's representative, if applicable) a sufficient opportunity to explain in detail all matters related to the clinical trial and to know all predictable results.

2) If consent cannot be obtained due to reasons such as lack of comprehension ability or intention expression ability of the study participant, the written consent of the representative is obtained. In this case, the consent of the representative shall not contradict the intention of the study participant. The representative of the study participant shall be the legal representative, in the order of spouse, direct continuation, and direct subordinate if there is no legal representative, but if there are several direct or direct descendants, it is determined by consultation.

3) The investigator must provide sufficient time for the study participant (representative, if necessary) to voluntarily decide on participation. Therefore, upon completion of the explanation, the subject (representative, if necessary) can decide whether to participate in the clinical trial in an independent space where the investigator and the investigator are not present (meaning to take time to consider it sufficiently), and the next possible visit It is recommended to be able to make decisions in the city.

4) The contents agreed by the study participant (representative if necessary) must be recorded in documents.

5) The investigator must confirm the participation of the study participant (representative, if necessary) in the clinical trial by signing the Informed Consent Form (Attachment 1)'. Investigators should not perform specific tests for the sole purpose of clinical trials until consent is obtained from the study participant (if necessary, an agent).

6) The investigator must confirm whether the study participant (representative if necessary) continues to participate in the clinical trial at each visit after obtaining written consent.

7) The investigator should emphasize that the subject (representative, if necessary) has the freedom to withdraw his/her consent to participation at any time without disadvantage or loss of the original interest.

8) When new information is identified that may relate to the study participant (representative, if necessary) willingness to continue participating in the clinical trial, the investigator shall inform the study participant (representative, if necessary) of this information in a timely manner.

13.3 Compliance with Ethics

Clinical trials should be conducted in accordance with the clinical trial protocol (including the subject's description and consent form) approved by the Institutional Review Committee and MFDS. Clinical trials should be performed in accordance with the items described in Section 11.1.

13.4 Study Participant Safety Protection Measures

Based on the Declaration of Helsinki, the investigator must carry out the clinical trial according to Section 11.1 with the rights and welfare of the subject in mind, and all investigators and investigators must accurately understand the clinical trial protocol and perform the clinical trial in compliance with the protocol do.

The Investigators must take precautions such as sufficient education for the clinical trials personnel, and promptly respond to the occurrence of adverse reactions and perform necessary reports.

13.5 Publication of Research Findings

Publication of the results of this trial will be allowed. Any proposed presentation, abstract and/or manuscript must be made available to GeneOne at least 60 days prior to submission. GeneOne shall have fifteen (15) days for review. If GeneOne considers that material would reveal protectable intellectual property, GeneOne may request a delay in submission for a maximum of three (3) months from the date of receipt in order for patent application(s) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

13.6 Quality Control and Reliability Assurance

Sponsors are responsible for verifying procedures and data for conducting clinical trials to protect subjects and ensure the reliability of clinical trial results.

The sponsor conducts an advance visit prior to the initiation of the clinical trial, and recruits subjects after the initiation visit. In order to ensure that clinical trials are performed in compliance with the matters described in Section 11.1, and clinical trial results can be recognized at the time of registration at home and abroad, the sponsor of the clinical trial may conduct monitoring and audit. The test manager agreed to conduct the inspection by signing this protocol.

At the monitoring visit, the sponsor will check against the supporting documentation to ensure that the clinical trial is being carried out in accordance with the approved protocol and items described in Section 11.1, and that the eCRF records are complete and clear. The investigator and the head of the clinical trial site (if applicable) must agree to and cooperate with the sponsor to directly access all relevant data and to devote time to the investigator oneself or the person concerned to discuss the problems found and related matters. .

The reguratory authority may also conduct an investigation at any time during the clinical trial or at the end of the clinical trial. In the case of inspection or investigation, the investigator (and the clinical trial site) allows the inspector and the investigator to directly access the relevant documents, and devotes the investigator himself or the person concerned to discuss the found problems and related matters and must agree and cooperate with what to do.

13.6 Approval of Clinical Trial Protocol

The clinical trials can be started after the clinical trial protocol and related documents are submitted to the MFDS and the Institutional Review Committee and approved.

13.6 Changes in Clinical Trial Protocol

Neither the investigator nor the sponsor may change the contents of this clinical trial protocol during the clinical trial without the consent of the other party. Once the test has begun, modifications should be made only in exceptional cases. Any changes to the clinical trial protocol must be signed and agreed in writing by all parties involved. Before conducting a clinical trial with the changed contents, the modified clinical trial protocol must be submitted to the MFDS and/or the Institutional Review Committee for approval.

13.6 Data and Safety Monitoring Board (DSMB)

In this clinical trial, an independent data and safety monitoring board (DSMB) is convened to evaluate the safety of subjects. The DSMB is convened at the request of investigators and sponsors, and carefully reviews safety data and immunogenicity data to evaluate the entry into phase 2.

The DSMB consists of the sponsor, the investigator of the laboratory, or its delegated person, and may include a clinical pharmacologist if necessary. Matters concerning the operation of the DSMB follow a separate plan.

14. INFORMATION OF THE PERSON WHO INTENDS TO CONDUCT THE CLINICAL TRIAL

14.1 Sponsor

GeneOne Life Science, Inc.

President & CEO: Young K. Park

Parc. 1 NH Finance Tower (Tower 2), 20th Floor

108 Yeoui-Daero

Yeongdeungpo-Gu, Seoul 07355, Korea

14.2 Principal Investigator

Role	Clinical Site	Position	Name
Principal Investigator (Cordinator)	TBD	TBD	TBD
Principal Investigator	TBD	TBD	TBD

14.3 Contract Research Organization

C&R Research

President & CEO: Moon Tae Yoon

06199, 412, Yeoksam-ro, Gangnam-gu, Seoul, Korea

15. OTHER MATTERS NECESSARY TO SAFELY AND SCIENTIFICALLY CONDUCT CLINICAL TRIALS

15.1 Clinical Trials Site

The head of a clinical trial site should equip the necessary facilities, professional manpower, and independent ethical institution for the execution of the relevant clinical trial at each stage of the

clinical trial, and make perfect preparations so that the relevant clinical trial can be properly carried out.

15.2 Principal Investigator and Clinical Site Staffs

The principal investigator and clinical site staffs should be fully aware of predicted adverse events and precautions for use through available information related to clinical investigational drugs, such as IB or drug attachments provided through the sponsor, and SAEs occurred during the clinical trial. In this case, the report shall be immediately reported to the Institutional Review Committee and the sponsor.

15.3 Protocol Violation

If it is known that the clinical trial protocol has been violated during the clinical trial, the investigator should notify the sponsor (or monitor) of the violation as soon as possible, and discuss and decide whether the subject continues to participate in the clinical trial.

In the case of dropout due to a serious clinical trial protocol violation (Section 4.4), all information collected up to the point of dropout and reasons for dropout should be collected in the eCRF.

15.4 Criteria for Treatment of Subjects after Clinical Trials

Treatment after the clinical trial for the subjects who dropped out of the clinical trial (Section 4.4) and those who completed the clinical trial should follow the general criteria for treatment and treatment.

However, if the subject is injured due to treatment or clinical procedures that would not have been received if they did not participate in this clinical trial, all treatments will be received according to the standard hospital procedures. Damage related to clinical trials will be borne by the sponsor in accordance with the sponsor's clinical trial victim compensation protocol and the terms and conditions of the sponsor's clinical trial compensation insurance.

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