Pontificia Universidad Católica de Chile
Facultad de Medicina
Departamento de Enfermedades Infecciosas e Inmunología Pediátrica
Facultad de Ciencias Biológicas
Departamento de Genética Molecular y Microbiología

**PROTOCOL TITLE:**

# Phase 3, double blind, placebo-controlled, randomized, multi-center study to evaluate the efficacy, safety and immunogenicity of an inactivated vaccine against the SARS-CoV-2 infection in high risk of infection adults 18 to 59 years old.

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| ***Protocol short name:*** | Coronavac03CL |
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| ***Date:*** | 25th July 2020 |
| ***Responsible Investigator:*** | Dra. Katia Abarca (Clinical team)<br>Dra. Susan Bueno (Scientific team) |
| ***Sponsoring Institution:*** | Pontificia Universidad Católica de Chile.<br>Avda. Libertador Bernardo O´Higgins 340, Santiago, Chile<br>Institución sin fines de lucro, educacional |
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| ***Designated representative:*** | Sr. Pedro Bouchon Aguirre<br>Vice Decano de Investigación<br>RUT: 8.608.860-6 |

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## 1. Background

Sinovac Life Sciences Co., Ltd. (Beijing, China) has worked in developing an inactivated SARS-CoV-2 vaccine since January 2020 in partnership with leading academic research institutes in China. The Company received approval from China's NMPA on April 13 to conduct phase I/II studies on its inactivated vaccine candidate against COVID-19 in China, after having demonstrated that the vaccine was safe and immunogenic in different animal models, including mice and non-human primates (Gao et al, Science 2020).

The phase I/II clinical trials were designed as randomized, double-blind and placebo-controlled studies. In total, 743 healthy volunteers, aged from 18 to 59 years old, enrolled in the trials. Of those, 143 volunteers participated in phase I and 600 volunteers in phase II. There was no severe adverse event (SAE) related to the vaccine reported in phase I/II trials. The phase II clinical trial results show that the vaccine induces neutralizing antibodies 14 days after the vaccination with a 0-14-day schedule. The neutralizing antibody seroconversion rate is above 90%, which concludes the vaccine candidate can induce positive immune response. The vaccination schedule determined in those studies will be two doses of 600 Standard Units (SU)/0,5 mL, separated by 14 days.

Considering the worldwide situation of the SARS-CoV-2 pandemic, it is necessary to promptly carry out multicenter clinical studies with vaccines that have completed phase 2 studies. The proposed study will allow efficacy assessment in a country with high level of viral circulation and different genetic population background than the Chinese population. Phase III clinical trials with this vaccine will be done in other countries apart from Chile (Brazil, Indonesia, Bangladesh and Turkey).

High-risk population to acquire the infection, as health personnel who works in hospitals attending COVID19 patients will be the target population for this study. In Chile, the rate of infection at mid-June is 997 cases/100,000 habs. (~1%), and in the Metropolitan Region of 1,600/100,000 habs. (~1.6%), with 179.436 confirmed cases and a fatality rate of 1.9%. In different health institutions, around 10-20% of health workers have been affected.

## 2. Objectives

**Primary objective**

- To evaluate the efficacy of a two-dose regimen of SARS-CoV-2 inactivated vaccine against RT-PCR confirmed symptomatic COVID-19.

**Secondary objectives**

- To evaluate efficacy of at least one dose of SARS-CoV-2 inactivated vaccine against RT-PCR confirmed symptomatic COVID-19.
- To evaluate efficacy of a two-dose regimen of SARS-CoV-2 inactivated vaccine against COVID-19 hospitalization cases.
- To evaluate efficacy of SARS-CoV-2 inactivated vaccine against COVID-19 severe or death cases.
- To evaluate the safety of SARS-CoV-2 inactivated vaccine.
- To evaluate the immunogenicity of SARS-CoV-2 inactivated vaccine.

**Exploratory objectives**

- To evaluate the vaccine immune enhancement of disease.

See definitions in Section 3.2.

## 3. Study design

This is a phase 3 randomized, double blind, placebo-controlled study in adults 18-59 years old of box sex with high risk of SARS-CoV-2 infection to be enrolled and randomly assigned into 2 groups at a ratio of 1:1 to receive 2 doses of vaccine or placebo in an interval of 14 days. All subjects will be followed-up for 12 months after the first dose.
For the study population, and adaptive design will be done: starting with 3,000 health workers in this phase and adding, if necessary, a second phase with other 2,000 high risk of infection persons (eg, more health workers, some high incidence counties inhabitants, etc.).
Since the 4$^{th}$ month of follow up, the DSMB will evaluate regularly (once a month) the number of reported COVID19 cases; if they are less than expected, a second phase with other 2,000 participants will be implemented.
In addition, the DSMB will perform blinded interim analysis regularly (once a month) since the 4$^{th}$ month of follow up, to determine if with the reported Covid19 cases it is possible to determine efficacy, and to decide whether the clinical trial should finish early. In that case, the safety and immunogenicity follow up will be completed.

**Duration of the study:** 12 months after the first dose of vaccine/placebo.
**Study visits:** a selection visit, and 7 remote or at the clinic visits (details in Section 6 and Tables N°1 and N°2)
**Vaccination Schedule:** two doses of vaccine/placebo at days 0 and 14
**Data collection:** data will be collected through an electronic Case Report Form (eCRF)
**Follow-Up:** all participants will be evaluated and follow up for safety and efficacy. A subgroup of 300 subjects will be follow-up for immunogenicity (225 from the study vaccine arm and 75 from the placebo arm).
Details of safety, immunogenicity and efficacy follow-up, operational definitions, and end points, in Section 7.

## 4. Study population

In the first part of the study, the study population will consist on 3,000 health workers aged from 18 to 59 years, male and female (similar proportions of each gender), who have not had a documented previous SARS-CoV-2 infection and does not have serum SARS-CoV-2 IgG antibodies (seronegative), are not currently infected (negative RT-PCR), and are not HIV infected (negative HIV ELISA test). Female subjects of reproductive potential must use birth control measures for at least the first 8 weeks after the second vaccination. Pregnancy test must be negative before each vaccine dose.
Subjects with immunosuppression will not be included.

If at the 4 months' follow-up, an insufficient COVID19 cases have been recorded, a second group of 2,000 participants will be enrolled. This group will be selected using incidence rates available at that moment (more health workers, people living in counties with high incidence of COVID19 cases, etc.).
A Protocol Amendment with a new version of the Protocol and Informed Consent will be issued if the second phase is decided.

**4.1. Inclusion Criteria (for the first phase)**

- Health worker adults, men and women, aged 18-59 years' old without current or previous SARS-CoV-2 infection
- Able to understand and sign the informed consent form
- Able to comply with all the study procedures and visits

**4.2 Exclusion criteria**

- History of SARS CoV-2 confirmed infection;
- Serum anti SARS CoV-2 IgG positive;
- Positive RT-PCR for SARS CoV-2 at enrolment;
- HIV infection documented by an ELISA test or risk factor for acquisition during the window period (through a short questionnaire);
- For females: Pregnancy (confirmed by positive beta-hCG test or by rapid urine test), breastfeeding or intent to engage in sexual relations with reproductive intent without use of birth control methods in the three months following vaccination;
- Known allergy to components of the study vaccine or control;
- Use of immunosuppressant therapy regimens within the six months prior to enrollment in the study or planned use within the two years following enrollment. Immunosuppressant therapy regimens include: antineoplastic chemotherapy, radiation therapy and immunosuppressants to induce transplant tolerance, among others；
- Use of immunosuppressive doses of corticosteroids within the three months prior to the enrollment in the study and planned use of immunosuppressive doses of corticoids within the three months following enrollment in the study. Immunosuppressive doses of corticosteroids will be considered the equivalent prednisone 20 mg/day for adults, for longer than one week. Continued use of topical or inhaled corticosteroids is not considered an immunosuppressant;
- History of asplenia;
- History of bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture;
- Any alcohol or drug abuse over the 12 months prior to enrollment in the study that has caused medical, professional or family problems, indicated by clinical history;
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate;
- Participation in another clinical trial with an investigational product in the six months prior to enrollment in the study or planned participation in another clinical trial within the two years following enrollment;
- Received live attenuated virus vaccine or inactivated vaccine within the 28 days or 14 days, respectively, prior to enrollment in the study, or immunization planned within the 28 days after enrollment in the study;
- Fever (axillary temperature >37.5℃) within the past 24 hours;
- Any other condition that, in the opinion of the principal investigator or his/her representative physician, could put the safety/rights of potential participants at risk or prevent them from complying with this protocol.

Note: well-controlled chronic medical conditions are allowed (as diabetes, arterial hypertension, asthma) as well as smoking and obesity.

## 5. Study Vaccine and Placebo

Each subject will receive two doses of 0,5 ml in the non-dominant deltoid area of the study vaccine or placebo, with a 14 days' interval between doses.
Both products have been manufactured by Sinovac Life Sciences Co., Ltd.
Address: N°39 Shangdi Xi Road, Haidian District, Beijing, PRC.

### 5.1. Investigational vaccine

Study vaccine composition:
SARS-CoV-2 vaccine (Vero cell) inactivated contains inactivated SARS-CoV-2 antigen, aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride. No preservative is present in this product.
0,5 mL/syringe per dose. One pre-filled syringe per box
Description: a milky white suspension
Storage and transport at +2 to +8°C and protect from light. Do not freeze.

### 5.2. Placebo control

Placebo composition:
Placebo contains aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride. No preservative is present in this product.
0,5 mL/syringe per dose. One pre-filled syringe per box
Description: a milky white suspension
Storage and transport at +2 to +8°C and protect from light. Do not freeze.

### 5.3. Vaccine/placebo administration:

A non-blind study nurse will be responsible for the administration of the vaccine to subjects enrolled into the study according to the protocol procedures. All vaccines/placebo will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations. These personnel will not perform any safety or efficacy follow-up.

## 6. Study Procedures

Informed consent must be obtained from the subject prior to the performance of any trial specific tests or evaluations.

**Screening Visit. AT THE CLINIC (Selection) (-5 to -2 d):**

a. Explain, discuss and obtain signature of the informed consent document from the subject (by investigator or a qualified designee of the investigator (physician) before first dose of vaccine/placebo)
b. Demographic data, significant medical history and concomitant medication information
c. Details of high-risk criteria: type of health work, unit of work, period of time working since March 2020
d. Physical exam, including a check of general appearance and systems evaluation. Subject's vital signs, blood pressure, height/weight (IBM calculation), axillary or orally temperature. The physical assessment will be performed by the investigator or by a qualified designee of the investigator (physician)
e. Review with females of childbearing potential their ability to become pregnant and commitment to practice appropriate birth control at least for 3 months after study entry (2 months after second dose). If sexually active, all participants must have been using one of the accepted birth control methods for at least two months prior to study entry

f. Inclusion and exclusion criteria evaluation
g. Blood sample for serology (anti SARS-CoV-2 IgG antibodies), HIV ELISA, and pregnancy test (30 mL)
h. Nasopharyngeal sample for COVID19 RT-PCR
i. Schedule Visit 1 (D0)

**Visit 1. AT THE CLINIC. Study Day 0 (first dose of vaccine/placebo)**

a. Update of medical history and concomitant medication (including any analgesic/antipyretic medication 24 hours prior to study vaccination) and screening test results
b. Physical examination, including vital signs and axillary or orally temperature
c. Inclusion and exclusion criteria evaluation. If the subject meets all inclusion and none exclusion criteria and is confirmed for study enrolment, assign the subject number
d. Randomization for vaccine/placebo and allocation of the immunogenicity group
e. Obtain a blood sample (30 mL) via venipuncture from subjects of the immunogenicity group
f. Vaccine administration: a qualified unblended study nurse will administer the assigned vaccine intramuscularly in the subject's deltoid area of the non-dominant arm
g. Observation of the subject for at least 30 minutes, examination of the vaccination site for any local reactions, subject body temperature, evaluation of any systemic reactions and other AEs
h. Give to the subject a thermometer and a ruler to be used for the duration of the study and instruct him/her in its use
i. Dispense Dairy Card N°1 for the next 7 days (D0-6) and instructions for register and reporting via remote application information concerning to: - local and systemic AE, including axillary temperature (solicited AE), AE (unsolicited AE), concomitant medications; - recording Diary Card information at approximately the same time each day for documenting local and systemic reactions
j. Dispense a Follow-up Form N°1 (D7-13) to record: - AE; - SAE; - concomitant medications; - any SARS-CoV-2 symptoms or close contact with a confirmed case; and instructions to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms or close contact with a confirmed case
k. Schedule Visit 2 (D7) (remote)

**Visit 2. REMOTE: Study Day 7 (± 2, 7 days after first dose of vaccine/placebo**)

a. Dairy Card N°1 (D0-6) information is sent by the participant through remote application (via computer or mobile phone)
b. The site personnel review the information, confirm completeness of solicited and unsolicited AEs, concomitant medications, SARS-CoV-2 symptoms and close contact with a recently confirmed COVID19 case
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 3 (D14) (at the clinic) by the study application

**Visit 3. AT THE CLINIC: Study Day 14 (± 3, 14 days after first dose) – Second dose of vaccine/placebo**

a. Follow Up Form N°1 (D7-13) information is sent by the participant through remote application (via
computer or mobile phone) or during the visit
b. The site personnel review the information, and confirm completeness

c. Medical history and brief physical evaluation, including measurement of vital signs and axillary temperature. Verify the if the subject has taken any analgesic/antipyretic medication prior to study vaccination
d. Vaccine administration: a qualified study nurse will administer the assigned vaccine intramuscularly in the subject's deltoid area of the non-dominant arm
e. Observation of the subject for at least 30 minutes, examination of the vaccination site for any local reactions, subject body temperature, evaluation of any systemic reactions and other AEs
f. Dispense a Dairy Card N°2 for the next 7 days (D14-20) with instructions for register and reporting via remote application information concerning to: - local and systemic AE, including axillary temperature, other AEs, concomitant medications; - completion of the Diary Card at approximately the same time each day for documenting local and systemic reactions; - instruct subjects to be sure de Dairy Card content is completely filled
g. Dispense a Follow-up Form N°2 (D21-41), to record: - AE; - SAE: - relevant concomitant medications (a list of this medications included); - any SARS-CoV-2 symptoms or close contact with a confirmed case; and instructions to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms or close contact with a confirmed case
h. Dispense a Follow-up Form N°3 (D42-179) and N°4 (D180-360) for the non-immunogenicity group, to record: - SAE; - relevant concomitant medications (a list of this medications included); - any SARS-CoV-2 symptoms or close contact with a confirmed case; and instructions to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms or close contact with a confirmed case
i. Schedule Visit 4 (D21) (remote)

**Visit 4. REMOTE: Study Day 21 (± 3, 7 days after second dose of vaccine/placebo**)

a. Dairy Card N°2 (D14-20) information is sent by the participant through remote application (via computer or mobile phone)
b. The site personnel review the information, confirm completeness of AEs, concomitant medications, SARS-CoV-2 symptoms and close contact with a recently confirmed COVID19 case
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 5 (D42) (at the clinic for the immunogenicity group and remote for the non-immunogenicity group) by the study application

**Visit 5. AT THE CLINIC: Day 42 (± 7, 28 days after second dose). For the immunogenicity group**

a. Follow-up Form N°2 (D21-41) information is sent by the participant through remote application (via computer or mobile phone) or during the visit
b. The site personnel review the information, and confirm completeness
c. Medical history (including symptoms of COVID19 and contact with a confirmed case) and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (30mL) via venipuncture
e. Dispense the Follow-up Form N°3 (D42-179), to record: - SAE, relevant concomitant medications (a list of this medications included); - any SARS-CoV-2 symptoms or close contact with a confirmed case; and instructions to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms or close contact with a confirmed case

f. Schedule Visit 6 (Day 180)

**Visit 5. REMOTE: Day 42 (± 7, 28 days after second dose). For the non-immunogenicity group**

a. Follow-up Form N°2 (D21-41) information is sent by the participant through remote application (via computer or mobile phone)
b. The site personnel review the information and confirm completeness
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 5 (at the clinic for the immunogenicity group and remote for the non-immunogenicity group) by the study application
f. Schedule Visit 6 (remote)

**FOLLOW-UP PERIOD 1. REMOTE (Days 43-179)**

a. Follow-up Form N°3 (D42-179) information is sent by the participant through remote application (via computer or mobile phone) at any moment they present SAE, use of relevant medication, SARS-CoV-2 symptoms or close contact with a confirmed case
b. The site personnel contact the subject by phone if needed to complete information
c. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable

**VISIT 6. AT THE CLINIC: Study Day 180 (14±, 6 months after first dose of vaccine/placebo) – For the Immunogenicity group**

a. Complete Follow-up Form N°3 (D42-179) is sent by the participant through remote application or at the site visit
b. The site personnel review the information and confirm completeness
c. Medical history and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (30mL) via venipuncture
e. Dispense the Follow-up Form N°4 (D180-360), to record: -SAE, relevant concomitant medications (a list of this medications included); - any SARS-CoV-2 symptoms or close contact with a confirmed case; and instructions to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms or close contact with a confirmed case
f. Schedule Visit 7 (D360) last visit

**Visit 6. REMOTE: Day 180 (14±, 6 months after first dose of vaccine/placebo). For the non-immunogenicity group**

a. Complete Follow-up Form N°3 (D42-179) information is sent by the participant through remote application (via computer or mobile phone)
b. The site personnel review the information and confirm completeness
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 7 (D360) last visit

**FOLLOW-UP PERIOD 2. REMOTE (Days 180-360)**

a. Follow-up Form N°4 (D180-360) information is sent by the participant through remote application (via computer or mobile phone) at any moment they present SAE, use of relevant medication, SARS-CoV-2 symptoms or close contact with a confirmed case
b. The site personnel contact the subject by phone if needed to complete information
c. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable

**VISIT 7. AT THE CLINIC: Study Day 360 (14±, 12 months after first dose of vaccine/placebo)**

a. Complete Follow-up Form N°4 (D180-360) is sent by the participant through remote application or at the site visit
b. The site personnel review the information and confirm completeness
c. Medical history and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (30mL) via venipuncture for the immunogenicity subgroup
e. Study close

**Table 1. Summary of Study procedures for the Immunogenicity group**

| **Visit** | **Screening Visit** | **Visit 1 At the clinic** | **Visit 2 Remote** | **Visit 3 At the clinic** | **Visit 4 Remote** | **Visit 5 At the clinic** | **Follow-Up Remote** | **Visit 6 At the clinic** | **Follow-Up Remote** | **Visit 7 At the clinic** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Procedures and Evaluations/Days** | **-5 to -2** | **D0 Dose1** | **D7** | **D14 Dose2** | **D21** | **D42** | **D42-179** | **D180** | **D181-359** | **D360** |
| **Enrolment** | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | |
| Demographic data | X | | | | | | | | | |
| Medical History | X | X | | X | | x | | X | | X |
| Physical Examination | X | X | | X | | X | | X | | X |
| Vital signs | X | X | | X | | | | | | |
| SARS CoV-2 IgG Screening | X | | | | | | | | | |
| HIV screening (ELISA) | X | | | | | | | | | |
| Pregnancy test (serum)* | X | | | | | | | | | |
| SARS CoV-2 RT-PCR | X | | | | | | | | | |
| Inclusion/Exclusion criteria evaluation | X | X | | X | | | | | | |
| **Investigation product** | | | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Vaccination (vaccine/placebo) | | X | | X | | | | | | |
| **Safety** | | | | | | | | | | |
| Pregnancy test (urine)* | | | | X | | | | | | |
| Post vaccination AE** | | X | | X | | | | | | |
| Solicited & Unsolicited AE, CM | | X | X | X | X | | | | | |
| Other AE | | | | | | X | | | | |
| Relevant CM | | | | | | X | X | X | X | X |
| Serious Adverse Event (SAE) | X | X | X | X | X | X | X | X | X | X |
| Enhanced disease | | X | X | X | X | X | X | X | X | X |
| **Efficacy** | | | | | | | | | | |
| Efficacy assessment by clinical data and SARS CoV-2 RT-PCR when correspond | | X | X | X | X | X | X | X | X | X |
| **Immunogenicity** | | | | | | | | | | |
| Antibodies to SARS-2<br>Cellular immune response to SARS-2 | | X | | | | X | | X | | X |
| **Safety & Efficacy Registration** | | | | | | | | | | |
| Type of Registration Form | | | Dairy Card N°1 D0-6 | Follow-Up Form N°1 D7-13 | Dairy Card N°2 D14-20 | Follow-Up Form N°2 D21-41 | Follow-Up Form N°3 D42-179 | | Follow-Up Form N°4 (180-360) | |

CM: concomitant medications; AE: adverse events
*All female subjects of childbearing potential must test negative for pregnancy during screening and at visits prior to study vaccine administration.
**Subjects will be observed for at least 30 minutes after the administration of study vaccine for local and general symptoms or reactions.

**Table 2. Summary of Study procedures for the non-immunogenicity group**

| **Visit** | **Screening Visit** | **Visit 1 At the clinic** | **Visit 2 Remote** | **Visit 3 At the clinic** | **Visit 4 Remote** | **Visit 5 Remote** | **Follow-Up Remote** | **Visit 6 Remote** | **Follow-Up Remote** | **Visit 7 At the clinic** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Procedures and Evaluations/Days** | **-5 to -2** | **D0 Dose1** | **D7** | **D14 Dose2** | **D21** | **D42** | **D42-179** | **D180** | **D181-359** | **D360** |
| **Screening/Enrolment** | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | |
| Demographic data | X | | | | | | | | | |
| Medical History | X | X | | X | | | | | | X |
| Physical Examination | X | X | | X | | | | | | X |
| Vital signs | X | X | | X | | | | | | |
| SARS CoV-2 IgG Screening | X | | | | | | | | | |
| HIV screening (ELISA) | X | | | | | | | | | |
| Pregnancy test (serum)* | X | | | | | | | | | |
| SARS CoV-2 RT-PCR | X | | | | | | | | | |
| Inclusion/Exclusion criteria evaluation | X | X | | X | | | | | | |
| **Investigation product** | | | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Vaccination (vaccine/placebo) | | X | | X | | | | | | |
| **Safety** | | | | | | | | | | |
| Pregnancy test (urine)* | | | | X | | | | | | |
| Post vaccination AE** | | X | | X | | | | | | |
| Solicited & Unsolicited AE, CM | | X | X | X | X | | | | | |
| Other AE | | | | | | X | | | | |
| Relevant CM | | | | | | X | X | X | X | X |
| Serious Adverse Event (SAE) | X | X | X | X | X | X | X | X | X | X |
| Enhanced disease | | X | X | X | X | X | X | X | X | X |
| **Efficacy** | | | | | | | | | | |
| Efficacy assessment by clinical data and SARS CoV-2 RT-PCR when correspond | | X | X | X | X | X | X | X | X | X |
| **Safety & Efficacy Registration** | | | | | | | | | | |
| Type of Registration Form | | | Dairy Card N°1 D0-6 | Follow-Up Form N°1 D7-13 | Dairy Card N°2 D14-20 | Follow-Up Form N°2 D21-41 | Follow-Up Form N°3 D42-179 | | Follow-Up Form N°4 (180-360) | |

CM: concomitant medications; AE: adverse events; SAE: serious adverse events
*All female subjects of childbearing potential must test negative for pregnancy during screening and at visits prior to study vaccine administration.
**Subjects will be observed for at least 30 minutes after the administration of study vaccine for local and general symptoms or reactions.

## 7. Efficacy, Safety and Immunogenicity Evaluation

### 7.1. Evaluation and follow-up

**Safety:** All vaccinated subjects will be observed on site for immediate adverse events (AEs) for 30 minutes after vaccination. Solicited local or systemic AEs occurring ≤7 days after each dose will be recorded in a Daily Cards (D0-6 and D14-20), unsolicited AEs occurring ≤28 days (D0-28) and SAE occurring ≤12 (D21-360) months after vaccination will be recorded in Follow-up Forms. Daily Cards and Follow-up Forms will be sent by participants through a remote application and reviewed for completeness by the study team.
All SAE must be reported to the Sponsor's Security Delegate, ethics committee, Sinovac, CRO, and DSMB within 24 hours from the date when the study site team becomes aware of the event. The Sponsor's Security Delegate will report any SAE to the Public Health Institute (ISP) within 48 h of being notified.
An independent Data Safety Monitoring Board (DSMB) will assess the safety and reactogenicity data of the first 100 subjects when they complete a 7 day of follow up after each vaccine dose. The DMSB is empowered to halt the trial temporarily and prevent further vaccination in case the analysis indicates considerable safety issues.

**Efficacy:** subjects will be followed up until 12 months after the first dose to identify and register any SARS-CoV-2 infection. COVID19 symptoms and close contact with confirmed cases will be collected through a Follow-up Form and in in-site visits. Participants that fulfill the suspected case definition (see definition below) and those who have been in close contact (see definition below) of a confirmed case will be promptly studied by RT-PCR in nasopharyngeal (NP) sample. If this RT-PCR results negative, a second one will be performed in the following 48 h.

Participants with SARS-CoV-2 infection will be evaluated by study staff and they will receive the driving directions that correspond to their particular clinical situation. If necessary, they may be referred to specialists from the institution at no cost to them. Their evolution will be closely monitored by the research personnel until the resolution of the picture, the same will be done in the case of hospitalization.

COVID19 case monitoring will be conducted after the final vaccination and the cases collected 14 days after final vaccination will be considered valid cases for efficacy analysis.
An independent Data Safety Monitoring Board (DSMB) will assess the efficacy data of the first 4 months of follow up. If there is less COVID19 cases that needed for efficacy confirmation, a second phase with 2,000 new participants will be set up. An Amendment to this Protocol will be submitted to the ethics committee in such case.
Efficacy follow-up will stop if an interim analysis (performed monthly since the 4$^{th}$ month of follow up) shows that the efficacy end point is already fulfilled. In that case, all participants who received placebo, will be vaccinated.

**Immunogenicity:** blood samples will be collected from participant in a subgroup of 300 out of the first 3,000 participants (225 from the study vaccine arm and 75 from de placebo arm) at D0 (first dose day, baseline), D42 days (28 days after the second dose) to determine the neutralizing antibody level, percentage of seroconversion, and cellular immunity; and at D180 and D360 for determine persistence of immune response.

**Remote follow up:** due to pandemic block-outs, the majority of visits will be remote, using an application for the participant's register and sending the needed information to the eCRF. Regular reminders will be sent by this application. At any suspected case of COVID19 or close contact with a confirmed case, an in-site visit will be scheduled in the next 24h to perform a RT-PCR for SARS-CoV-2 by NP swab.

### 7.2. Efficacy Analysis

#### 7.2.1. Efficacy Endpoints:

All end points will be compared between vaccinated and placebo recipients

- Number of cases of SARS-CoV-2 infection confirmed by PCR from 14 days after the second dose of vaccine
- Number of cases only received one dose of SARS-CoV-2 infection confirmed by PCR from 14 days after vaccine
- Number of cases of clinically diagnosed SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of hospitalized cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of pneumonia cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of severe or death cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine

#### 7.2.2. Exploratory endpoint: enhanced disease

Considering that there is no operational definition to diagnose this hypothetical situation, this end point will be evaluated by comparing the severity of COVID19 between the vaccine group and placebo to assess whether the vaccine protects or increases the severity of the disease. In case that among those vaccinated there is a more severe disease (using the severity criteria indicated later in the next section (operational definitions) it may be concluded that the vaccine exacerbates the disease.

#### 7.2.3. Efficacy Operational definitions

**Suspected COVID-19 case:**

- At least two of the following symptoms: chest pain, chills, nasal congestion, myalgia, headache, sore throat, fatigue, vomiting, diarrhea, loss of smell (anosmia), loss of taste (ageusia)
  OR
- At least one of the following symptoms: fever, cough, shortness of breath, difficulty breathing
  OR
- radiographic evidence of pneumonia

**Close contact definition** (Resolution N°403 of the Chilean Ministry of Health, 28th May 2020):
A person who has been in contact with a confirmed case with COVID19, between 2 days before the onset of symptoms and 14 days after the onset of symptoms of the confirmed case. For persons without symptoms, contact should have occurred within 14 days of taking the RT-PCR test. In both cases, to qualify such contact as close, one of the following circumstances must also be met:

- More than 15 minutes of face-to-face contact, less than one mete
- Having shared a closed space for 2 hours or more, in places such as offices, jobs, meetings, schools, among others
- Live or spend the night in the same home or places similar to home, such as hostels, boarding schools, closed institutions, nursing homes, hotels, residences, among others
- Have moved in any closed means of transport within a proximity of less than one meter with another occupant of the means of transport who is infected.

**RT-PCR confirmed symptomatic COVID-19:**

- At least two of the following symptoms: chills, nasal congestion, myalgia, headache, sore throat, fatigue, vomiting, diarrhea, loss of smell (anosmia), loss of taste (ageusia)
  OR
- At least one of the following symptoms: fever, cough, shortness of breath, difficulty breathing
  OR
- radiographic evidence of pneumonia
  AND
- No alternative more likely diagnosis
  AND
- Detection of SARS-COV-2 RNA in a clinical specimen using RT-PCR detection test

**Clinically diagnosed SARS-CoV-2 infection:**
The same as before, but with a RT-PCR for SARS-COV-2 negative, indeterminate or not performed

**Pneumonia case of SARS-CoV-2 infection:**
Clinical signs of pneumonia (fever, cough, shortness of breath, difficulty breathing) plus radiologic features consistent with the viral infection: ground-glass opacity and bilateral patchy shadowing sometimes with a rounded morphology and a peripheral lung distribution.

**Severity criteria of RT-PCR confirmed symptomatic COVID-19:**

- Mild Disease: Symptomatic patients without viral pneumonia or hypoxia
- Moderate Disease: Clinical signs of pneumonia (fever, cough, shortness of breath, difficulty breathing) but no signs of severe pneumonia, SpO2 $\geq$ 90% on room air
- Severe disease: Clinical signs at rest indicative of severe clinical illness (RR>30/min, HR>125/min, sat < 93% at room air at sea level, PaO2/FiO2 < 300 mm Hg); respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO); evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors) o Significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; death

Any detected COVID19 case will be reported in this trial and in the National Surveillance System (Epivigila) and will be treated and managed according to the Chilean Guidelines. Clinical management of cases will be providing for the participant 'own health system. A close follow-up of the outcome of any COVID19 case will be done by the study team, registering new symptoms, severity grading, therapies, hospitalization, intensive care admission, complications, mechanical ventilation use, sequelae and death.

### 7.3. Safety Analysis

#### 7.3.1. Safety Endpoints

- Incidence of local (pain, induration, swelling, redness, pruritus) and systemic (diarrhea, anorexia, vomiting, nausea, muscle pain (non-inoculated site), arthralgia, headache, cough, fatigue, pruritus (non-inoculated site), skin rash (exanthema), allergic reaction, fever (axillary temperature)) solicited reactions during 7 days after each dose of the vaccine
- Incidence of any adverse event (AE) within 28 days after the vaccination
- Incidence of SAE until 6 months after the first dose of the vaccine
- SAE or AE leading to withdrawal from the study
- Concomitant medications within 7 days after each dose of vaccination
- Relevant concomitant medications (immunosuppressive drugs) from D28 to the end of the study

#### 7.3.2. Adverse Events Definitions, Severity Grading and Study Vaccine Relationship:

**Adverse Events:** an adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.
An unexpected adverse event is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.
All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and medical monitor whether continued follow-up of the AE is warranted.

**Severity of AE:** The severity of solicited AE will be graded through a numeric scale of 1 to 4, as per Table 3 (local events) and Table 4 (systemic events), created based on the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" guide of the Food and Drug Administration of the United States (FDA), the "Common Terminology Criteria for Adverse Events - Version 5.0" of the National Cancer Institute of the United States (NCI/NIH) and the "Guidelines for grading scale of adverse events in vaccine clinical trials" of the National Medical Products Administration, China.

**Table 3. Severity grading criteria for local adverse events**

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Pain | Not affecting or slightly affecting physical activity | Affecting physical activity | Affecting daily life | Loss of basic self-care ability, or hospitalization |
| Induration# | Diameter 2.5 to <5 cm without affecting or slightly affecting daily life | 5 to <10 cm in diameter or affecting daily life | Diameter ≥10 cm or ulceration or secondary infection or aseptic abscess or wound drainage or seriously affecting daily life | Abscess, exfoliative dermatitis, dermal or deep tissue necrosis |
| Swelling # | Diameter 2.5 to <5 cm without affecting or slightly affecting daily life | 5 to <10 cm in diameter in area or affecting daily life | Diameter ≥10 cm or ulceration or secondary infection or aseptic abscess or wound drainage or seriously affecting daily life | Abscess, exfoliative dermatitis, dermal or deep tissue necrosis |
| Redness# | Diameter 2.5 to <5 cm without affecting or slightly affecting daily life | 5 to <10 cm in diameter in area or affecting daily life | Diameter ≥10 cm or ulceration or secondary infection or aseptic abscess or wound drainage or seriously affecting daily life | Abscess, exfoliative dermatitis, dermal or deep tissue necrosis |
| Pruritus | Itching at injection site, relieved within 48 hours | Itching at injection site, did not alleviate within 48 h after treatment | Affecting daily life | NA |

# The maximum measured diameter or area should be used for induration and swelling, and red; evaluation and grading should be based on functional grade and actual measurement results, and higher grading indicators should be selected.

**Table 4. Severity grading criteria for systemic adverse events and vital signs**

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Diarrhea | Mild or transient, 3-4 times/day, abnormal stool | Moderate or persistent, 5-7 times/day, abnormal stool | >7 times/day, abnormal stool, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, requiring intravenous infusion >2L | Hypotensive shock, hospitalization |
| Anorexia | Decreased appetite, not affecting food intake | Decreased appetite, reduced food intake, not affecting body weight | Decreased appetite, and significantly reduced body weight | Need intervention (such as gastric tube feeding, parenteral nutrition) |
| Vomiting | 1-2 times/24 hours without affecting activity | 3-5 times/24 hours or affecting activity | >6 times within 24 hours or requiring intravenous fluid infusion | Hospitalization or other nutrition routes due to hypotensive shock |
| Nausea | Transient (<24 hours) or intermittent and basically normal food intake | Persistent nausea leads to reduced food intake (24-48 hours) | Persistent nausea leads to almost no food intake (>48 hours) or requires intravenous fluids | Life threatening (e.g., hypotensive shock) |
| Muscle pain (non-inoculated site) | Does not affect daily activities | Slightly affects daily activities | Severe muscle pain, seriously affects daily activities | Emergency or hospitalization |
| Arthralgia | Mild pain, not affecting daily activities | Moderate pain, requiring analgesics and/or pain interferes with functioning, yet not affecting daily activities | Severe pain, seriously affecting daily activities | Emergency or hospitalization |
| Headache | Not affecting daily activities, no treatment required | Transient, slightly affecting daily activities, may need treatment or intervention | Seriously affecting daily activities, need treatment or intervention | Intractability, need emergency or hospitalization |
| Cough | Transient, no treatment required | Persistent cough, effective treatment | Paroxysmal cough, uncontrolled treatment | Emergency or hospitalization |
| Fatigue | Normal activity is weakened <48 hours, without affecting the activity | Normal activity is weakened by 20%~50%>48 hours, slightly affecting the activity | Normal activity is weakened by >50%, seriously affecting daily activities, unable to work | unable to take care of oneself, emergency or hospitalization |
| Pruritus | Mild or localized; topical intervention indicated | Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral | Widespread and constant; limiting self-care activities of daily living or sleep; systemic corticosteroid or immunosuppressive therapy indicated | ----- |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | | intervention indicated; limiting instrumental activities of daily living | | |
| Skin rash (exanthema)† | Present, but asymptomatic | Symptomatic (pruritus/pain), but interferes only slightly with daily activities | Symptomatic, prevents daily activities | Emergency or hospitalization |
| Allergic reaction | Systemic intervention not indicated | Oral intervention indicated | Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated | Life-threatening consequences; urgent intervention indicated |
| **Vital Signs** | | | | |
| Fever (axillary temperature) | 37.6 a 37.9℃ | 38.0 a 38.4℃ | 38.5℃ a 39.4℃ | 39.5℃ o más |

†Specify if the skin rash is located in any specific body part or if it is widespread.

The severity of the unsolicited clinical adverse events will be classified through a numeric scale of 1 to 5, as per Table 5, which was created based on the "Guidelines for classification of adverse events in vaccine clinical trials" of the National Medical Products Administration, China.

**Table 5. Severity grading criteria for unsolicited adverse events.**

| | |
|---|---|
| **GRADE 1 (Mild)** | Transient (< 48 hours) or mild discomfort; no medical intervention/therapy required |
| **GRADE 2 (Moderate)** | Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required |
| **GRADE 3 (Severe)** | Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible |
| **GRADE 4 (Life-threatening)** | Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable |
| **GRADE 5** | Death |

**The relationship of the study treatment to an AE** will be determined by the investigator based on the following definitions:

- **Not Related:** the AE is not related if exposure to the investigational vaccine has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.
- **Possibly Related:** the administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational vaccine.

- **Probably Related:** the exposure to the investigational vaccine and AE are reasonably related in time and the investigational vaccine is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

**7.3.3. Serious Adverse Events Definition and Reporting:**

**Serious adverse event (SAE**):
Any untoward medical occurrence that:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs subject's hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

**SAE Reporting:**
All SAE will be reported to the institutional Ethics Committee, the Sponsor's Security Delegate, Sinovac, the DSMB and the CRO within one (1) calendar day from the date when the study site team becomes aware of the event. The initial notification must not be delayed even if the information is incomplete. Reporting of SAE will be completed preferably through the appropriate form that is included in the CRF system after assessment by a study doctor, or directly if it is not possible to access the CRF, mentioning the contact date and time of the first notification that was made by any means.
The Security Delegate of the sponsoring institution will be the Director of the Clinical Investigation Center Universidad Católica (CICUC), who has been delegated the responsibility of sending the security reports to the Public Health Institute (ISP), in the following 48 h of being notified.

**Pregnancies:**
To ensure subjects' safety, each pregnancy in a subject on study vaccine must be reported to the DSMB within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

### 7.4. Immunogenicity Analysis

#### 7.4.1 Immunogenicity Endpoints

- Seroconversion rate of IgG of SARS-CoV-2 at 28 days after the second dose (D42) of the vaccine
- Neutralizing antibody of SARS-CoV-2 at 28 days after the second dose (D42) of the vaccine
- GMT and GMI of IgG anti SARS-CoV-2 at 28 days after the second dose (D42) of the vaccine

**Exploratory immunogenicity end-points:**

- Cellular immunogenicity at 28 days after the second dose (D42) of the vaccine
- IgG antibodies and cellular immune response persistence at 180 and 360 days after the first dose of the vaccine

**Pairwise comparison:**

Pairwise comparisons related to the response after the second dose of vaccine and between vaccine and placebo will be performed in terms of:

• Ratio of GMTs
• Differences of seroconversion rates

**7.4.2. Immunogenicity Assays**

To evaluate the immune response to the study vaccine, the following assays will be performed in the immunogenicity group of 300 participants:

**Evaluation of the humoral immune response generated against SARS-CoV-2:**

- Humoral immune response based on total IgG: It will be determined by measuring serum IgG antibodies against Spike protein (S) and nucleoprotein (N). An ELISA test previously standardized by SINOVAC will be used, which will be provided by the company. As an alternative, the Euroimmune method will be used. ELISA anti SARS-CoV-2 (IgG) or Cobas ELECSYS anti SARS-CoV-2 will be used, depending on availability. For this, serum from subjects of the immunogenicity group will be obtained on days 0 and 42 (28 days after the second dose)
- Humoral immune response based on neutralizing antibodies: A SINOVAC standardized microtiter methodology will be used, which will be carried out in this company's offices. For this, serum from subjects of the immunogenicity group will be obtained on days 0 and 28 days post-second dose of vaccination (Day 42) will be sent to SINOVAC

**Evaluation of the cellular immune response generated against SARS-CoV-2**

- ELISpot and flow cytometry techniques will evaluate the T cell response in peripheral blood mononuclear cells of volunteer subjects at Day 0 (baseline state) and 28 days after the second dose. The mononuclear cells will be purified and exposed ex vivo to recombinant proteins S, N or to the complete inactivated virion. Antigenic peptides derived from these proteins will also be included. Specifically, secretion of IFN- γ will be measured by ELISpot (also called Interferon gamma release assay –IGRA). Additionally, the expression of activation markers and immunological memory in CD4 + / CD8 + T cells will be measured, including CD69, CD25, CD71, CD44, among others. As a negative control, the response against an irrelevant protein produced equivalently to viral proteins will be measured. In addition, CD4 + / CD8 + T cell staining will be included to measure intracellular IFN-γ expression in CD4 + / CD8 + T cells, followed by cell permeabilization and subsequent anti-IFN-γ antibody staining

**Evaluation of IgG antibodies persistence**

- Humoral and cellular response evaluation will be repeated at 180 and 360 days after the first dose for determining the persistence of antibodies

Humoral immune assays based on total IgG and cellular immune assays will be performed at the Laboratory of Biomedical Molecular Immunology, Virus, Inflammation and Microbial Patogenesis, Faculty of Biological Sciences.

## 8. Statistical Plan and Analysis

**Sample size**

Adaptive designs are used to calculate the sample size of this trial, and relevant parameters are set as follows:

- Protection rate of the vaccine $\mu$ =0.5
- The incidence rate in the high-risk population group: 6%
- α=0.05；
- 1-β=0.9；

At least 1,068 subjects will be recruited in each group. Considering 25% subjects will be missing during the test, the sample size in each group is 1,500. According to the enrolled subjects and the incidence rate in two groups, 90 COVID-19 cases are anticipated to be collected 6 months after vaccination. We would re-calculate the sample size if less than 20 cases were monitored within 2 months after vaccination

**Efficacy analysis**

The following indicators will be calculated according to the corresponding formula:

- The difference of incidence density between the vaccine and placebo group:

**Incidence density** = new cases in subjects with two vaccinations (the number of person year for subjects with two vaccinations) × 100%

- The protection ratio and effectiveness index of the vaccine for the prevention of COVID-19:

**Protection rate** =incidence density of placebo group - incidence density of vaccine group × 100%
**Protection index**=incidence density of placebo group - incidence density of vaccine group × 100%

**Primary endpoint (efficacy) calculation:**

- Incidence density and protection rate using number of cases confirmed by RT-PCR 14 days after the second dose of vaccine

**Secondary endpoints calculations:**

- Incidence density and protection rate using number of cases confirmed by RT-PCR 14 days after one dose of vaccine
- Incidence density and protection rate using hospitalization cases 14 days after the second dose of vaccine.
- Incidence density and protection rate using severe or death cases 14 days after the second dose of vaccine.
- Incidence of adverse reactions within 28 days after whole-schedule vaccination
- Incidence of solicited adverse reactions 7 days after each dose of vaccination
- Incidence of SAE within 6 and 12 months post the whole-schedule vaccination
- Concomitant medication 7 days after each dose of vaccination
- Relevant medication (immunosuppresive drugs) from D21 to the end of the study
- Seroconversion rate, seropositive rate, GMT and GMI 28 days after the second dose vaccination

## 9. Study Monitoring and Audits

Study monitoring and auditing will be performed in accordance with the local regulatory requirements. Investigators and their study staff will be trained on the study protocol and all applicable study procedures prior to subject enrollment. A CRF must be complete for each enrolled subject.

Study progress will be monitored by a Contract Research Organization (CRO) as frequently as necessary to ensure the rights and well-being of study subjects are protected, to verify adequate, accurate and complete data collection, protocol compliance and to determine that the study is being conducted in conformance with applicable regulatory requirements.

Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

## 10. Data Management

### 10.1. Data collection:

Most of the safety and efficacy information from participants will be collected through remote via. The rest will be collected at the in site visits.

An application will be set up for collecting data in the following forms:

- Dairy Card N°1: D0-6, for solicited and unsolicited AE, and concomitant medications registration 7 days after Dose 1 of the vaccine/placebo
- Dairy Card N°2: D14-20, for solicited and unsolicited AE, and concomitant medications registration 7 days after Dose 2 of the vaccine/placebo
- Follow Up Form N°1: D7-13, for AE and concomitant medications registration
- Follow Up Form N°2: D21-41, for AE and relevant concomitant medications registration
- Follow Up Form N°3: D42-179, for relevant concomitant medications registration
- Follow Up Form N°4: D180-360, for relevant concomitant medications registration

Besides this information, all these forms include notification of SAE, symptoms of COVID19 or close contact with a confirmed case, which must be registered and sent at the moment of presentation

The application will allow the participants to send the corresponding information at the time of the remote visit or when the mentioned situations present. Reminders will be sent via e-mail and mobile phone previous each visit (remote or at the clinic) and at regular periods of time in the follow up period for fill and send the forms.

All the collected information will be review for completeness and registered in an electronic CRF.

### 10.2. DSMB:

**Safety:** The DSMB will assess the safety and reactogenicity data of the first 100 subjects when they complete a 7 day of follow up after each vaccine dose. The DMSB is empowered to halt the trial temporarily and prevent further vaccination in case the analysis indicates considerable safety issues.

**Efficacy:** The DSMB will assess the blinded efficacy data monthly since the 4th month of follow up by an Interim Analyses. If there is less COVID19 cases that needed for efficacy confirmation, the second phase with 2,000 new participants will be set up (adaptive design).

**DSMB members:** this committee will be constituted by 5 independent experts, 3 physicians with experience in vaccine clinical trials, one statistician and one administrative secretary.

## 11. Ethics

### 11.1 Regulatory and Ethical Compliance:

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (Laws

19.628; 20.120; 20.584; 20.850 and the Chilean Sanitary Code, Law 20.850, that modifies the Chilean Sanitary Code), and with the ethical principles laid down in the Declaration of Helsinki.

**11.2 Informed Consent Procedures:**

Eligible subjects may only be included in the study after providing written and witnessed by a representative of the Institution Director, informed consent approved by the Institutional Ethics Committee

Informed consent must be obtained by trained medical study personnel, before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

**11.3. Protocol Amendments:**

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects.

An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes).

Protocol amendments must be approved by the IRB/IEC/REB.

As the study has an adaptive design, if the second phase with new 2,000 participants is decided, and Amendment and a new version of the Informed Consent will be submitted and approved by the Ethical Committee.

In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.

**11.4. Insurance and health coverage for possible damages**

There will be an Insurance to cover health attentions that may occur due to the presentation of any damage derived from the study vaccine.

The conditions are as follows: the insurer is responsible for paying the costs and expenses of the claimants with respect to any claim made by the research subjects for an injury caused by the trial (investigational product or study procedures). Insurance does not cover costs associated with acquiring a possible SARS-CoV-2 infection.

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