Protocol of Clinical Trial

An open-label clinical trial phase IIB to evaluate the immunogenicity and safety of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above that previously received one dose of Sputnik V

SHORT TITLE	Phase IIB Study of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above previously received one dose of Sputnik V
TRIAL ID	CS-nCoV-SeqAD26/FH 63
REGISTRATION No.	
STUDY VACCINE	Recombinant adenovirus 5 vectored COVID-19 vaccine (Ad5-nCoV)
VERSION	2.0
DATE	October 25th, 2021
SPONSOR	Fundación Huesped
PRINCIPAL INVESTIGATOR	Pedro Enrique Cahn, MD, Ph. D.

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1 LIST OF ABBREVIATIONS

Abbreviation	Full name
AE	Adverse Event
ATP	According-to-protocol
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Corona Virus Disease 2019
CRC	Clinical Research Coordinator
CRO	Contract Research Organization
DMP	Data Management Plan
EC	Ethic Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immune Sorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration, United States
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IM	Intramuscular Injection
IRB	Institutional Review Board
ITT	Intent-to-treat
MAE	Medically Attended AEs
NRA	National Regulatory Authority
PI	Principal Investigator
PPS	Per Protocol Set
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
SOP	Standard Operation Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
VP	Viral particles
WHO	World Health Organization

2 STATEMENT OF COMPLIANCE

2.1 Signature page of sponsor's approval for clinical trial protocol

Brief Title	Phase IIB Study of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above previously received one dose of Sputnik V
Official Title	An open-label clinical trial phase II B to evaluate the immunogenicity and safety of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above that previously received one dose of Sputnik V
Vaccine	Recombinant adenovirus 5 vectored COVID-19 vaccine (Ad5-nCoV)
Protocol Number	CS-nCoV-SeqAD26/FH 63
Protocol Date	October 25th, 2021
Version No.	2.0
Sponsor	Fundación Huesped
Sponsor Person In Charge	Pedro Enrique Cahn, PhD Director, Fundación Huésped Carlos Gianantonio 3932 (ex Pje. Ángel Peluffo) C1202ABB, Buenos Aires, Argentina Tel: (5411) 49817777 Fax: (5411) 49824024 E-mail: pedro.cahn@huesped.org.ar
Sponsor Person in Charge Signature:	Date:

2.2 Statement of PI

I agree to:

Take the full responsibilities as Principal Investigator (PI) of this clinical trial. Ensure that this clinical trial is conducted according to this approved protocol, or revised protocol, and the clinical trial SOPs from the sponsors.

Ensure that the investigators participating in this clinical trial understand the product information of investigational vaccine provided by the Sponsors, and understand the duties and responsibilities related to the clinical trial as outlined in this clinical trial protocol.

Ensure that there are no changes to the clinical trial protocol without the review and written approval of the sponsors and the Institutional Review Board (IRB) unless it is due to urgent removal of immediate damages to the participants or due to the regulatory requirements (such as due to administration requirements).

I fully understand the correct usage methods of the investigational vaccine, and I fully understand the information provided by the sponsors, including but not limited to the following: Current Investigator Brochure or equivalent documents.

I am familiar with and will comply with the requirements of Good Clinical Practices (GCP) and other relevant regulatory requirements.

Brief Title	Phase IIB Study of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above previously received one dose of Sputnik V
Protocol Number	CS-nCoV-SeqAD26/FH 63
Protocol Date	October 25th, 2021
Version No.	2.0
Principal Investigator	Dr. Pedro Enrique Cahn, MD, PhD

Signature:	Date:

3 LIST OF KEY ROLES

Key Roles/Duty	Responsible Individual	Organization
Sponsor	Pedro Enrique Cahn, MD, PhD	Fundación Huésped
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4 PROTOCOL SUMMARY

4.1 Synopsis

Full Title	An open-label clinical trial phase IIB to evaluate the immunogenicity and safety of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above that previously received one dose of Sputnik V
Brief Title	Phase IIB Study of Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) (Ad5-nCoV) in participants aged 18 years and above previously received one dose of Sputnik V
Trial ID	CS-nCoV-SeqAD26/FH 63
Study Phase	IIB
Study Center	Fundacion Huesped and additional sites
Location	Argentina
Objectives	**Primary objective:** To evaluate the neutralizing antibody titers in subjects that received one dose of Sputnik V and a second dose of Ad5-nCoV (with an interval of 21-180 days). **Secondary objectives:** To evaluate the safety profiles in adults aged 18 years and above that received Ad5-nCoV at least 21 days post-vaccination of one dose of Sputnik V. **Exploratory objectives** To evaluate if the neutralizing antibody titers in participants that received a 1st dose of Sputnik V plus a 2nd dose of Ad5-nCoV is non-inferior to that in participants vaccinated with two doses of Sputnik V.
Study design	This is an open-label , multicenter clinical trial.
Inclusion criteria	1. Participants aged 18 years and above at the time of randomization. 2. Provide written informed consent. 3. Axillary temperature ≤ 37℃. 4. Never received any investigational or licensed COVID-19 vaccine other than the 1st dose of Sputnik V with an interval of 21-180 days before the study.

	5. Subjects are eligible for immunization of this product as evaluated by investigators after medical history examination, physical examination and clinical judgment of health.
Exclusion criteria	1. Have a history of seizures, epilepsy, encephalopathy, psychosis. 2. History of anaphylaxis to any vaccine component. 3. Positive urine pregnancy test result, pregnant, lactation women, or intend to become pregnant within the next 6 months. 4. Congenital or acquired angioedema/neuroedema. 5. Medical history of Guillain-Barré syndrome. 6. Asplenia or functional absence of spleen. 7. Bleeding disorder (e.g. protein S or factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture. 8. Any confirmed or suspected immunosuppressive or immunodeficient status except from HIV infection; received immunosuppressive therapy, cytotoxic therapy, or chronic corticosteroids (excluding corticosteroid spray therapy for allergic rhinitis and surface corticosteroid therapy for acute non-complicated dermatitis) within the past 6 months, 9. History of chronic systematic infection. 10. Administration of immunoglobulins and/or any blood products within three months prior to the planned administration of the vaccine candidate. 11. Receiving anti-tuberculosis or cancer treatment. 12. History of laboratory-confirmed COVID-19 in the last 30 days, or positive result at the examination of SARS-CoV-2 antigen before vaccination. 13. Planned to receive any vaccine (licensed or investigational), other than the study intervention, within 14 days before and after study vaccination. 14. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban). 15. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, and affect the ability of the volunteer to participate in the study or impair interpretation of the study data.
Primary Endpoints	**Immunogenicity:** The Geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibody on Day 21 post-vaccination of Ad5-nCoV.
Secondary Endpoints	**Immunogenicity**: 1. The GMT of SARS-CoV-2 neutralizing antibody on Month 3 and Month 6 post-vaccination of Ad5-nCoV or the 2nd dose of Sputnik V.

	2. The GMT of S-protein receptor binding domain (S-RBD) antibody on Day 21, Month 3, and Month 6 post-vaccination of Ad5-nCoV or the 2nd dose of Sputnik V. **Safety**: 1. The incidence of solicited adverse reactions (ARs) within 7 days post-vaccination of Ad5-nCoV. 2. To evaluate the incidence of unsolicited adverse events (AEs) within 21 days post-vaccination of Ad5-nCoV. 3. The incidence of serious adverse events (SAEs) within 6 months post-vaccination of Ad5-nCoV.
Exploratory endpoints	1. The Geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibody on Day 21 post-vaccination of Ad5-nCoV and the 2nd dose of Sputnik V. 2. The SARS-CoV-2 specific T-cell response is studied using flow cytometry, evaluating the expression of activation markers in T CD4+ and CD8+ cells. Expression of CD40L (CD154), and the production of interferon γ (IFN-γ), interleukin-2 (IL-2) and tumoral necrosis factor (TNF-α) will be studied.
Sample Size	450
Target population	Healthy adults aged 18 years and above that received one dose of Sputnik V
Vaccines	Ad5-nCoV vaccine is a single-dose viral vector-based vaccine for preventing COVID-19 disease that was jointly developed by Beijing Institute of Biotechnology and CanSino Biologics Inc. Each dose contains 0.5 ml (5×10^{10} VP) replication-defective recombinant human type 5 adenovirus expressing S protein of SARS-CoV-2. A minimum of 0.4 mL is acceptable as a vaccination dose. Sputnik V comprises two different vector components, rAd26-S and rAd5-S, with a regimen of two-dose vaccination 21 days apart. The full dose of each shot contains 1×10^{11} VP in 0.5 ml liquid. The vaccine was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia.
Routes of Administration	Intramuscular Injection (IM)
Study design	This is an open-label and non-randomized study to demonstrate the immunogenicity and safety profile in adults that received the Ad5-nCoV vaccine at least 21 days but no later than 180 days after the first dose of Sputnik V. The non-inferiority hypothesis is used for the evaluation of the exploratory objective. The ratio of Geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibody in participants on Day 21 post-vaccination of Ad5-nCoV (previously received a 1st dose of Sputnik V) (Group A) and two doses of Sputnik V (Group B) is used for the

evaluation of this hypothesis. For sample size calculation, the α critical value was set as 2.5% (one-sided comparison) and power at 90%. If the neutralizing antibody test/reference ratio = 1 with a non-inferiority margin of 0.5 (setting the standard deviation to be 0.63), it is assumed to enroll about 100 subjects for each group. Additionally, 45 participants will be selected from Group A (to enter the immunogenicity subgroup for cellular immune response analysis. According to the above, considering extra subjects for compensating about 10% dropouts, the sample size of Group A is designed to be 450, for Group B is 200. Participants enrolled in Group A (1st dose of Sputnik V plus 1 dose of Ad5-nCoV) must have only received the 1st dose of Sputnik V and the interval between the previous injection (1st dose of Sputnik V) and the day of vaccination with Ad5-nCoV should be between 21 and 180 days. The comparator (Group B) will be the samples stored at the immunology lab of the Buenos Aires University Medical School, corresponding to individuals vaccinated with 2 doses of Sputnik V.

Table 1. Grouping information of the study

Group	Cohort	Primary immunization	Regimen	Sample size
Group A	One dose Sputnik V + one dose Ad5-nCoV	1st dose of Sputnik V	≥21 and ≤180 days on the day of enrollment	450
Group B	Two doses of Sputnik V	2 doses of Sputnik V	Stored samples as described above	200
Total	450			

Scheduled site visits

There are a maximum of 4 planned site visits in total,

Intervention	V1	V2	V3	V4
Follow-up time	Day 0	Day 21	Month 3	Month 6
Visit window		+3 days	±10 days	±15 days
Informed Consent	•			
Collect Demographic[g] and Participant Contact Information	•	•	•	•
Physical examination (height, weight, vital signs, body temperature, resting pulse and blood pressure)	•			

	Urine Pregnancy test [a]	•			
	Check medical history and inclusion and exclusion criteria	•			
	SARS-CoV-2 antigen assay [b]	•			
	Enrollment [c]	•			
	Blood collection [f]	•	•	•	•
	Vaccination	•			
	Collection of diary/contact card		•		
	SAE review [d&e]	•	•	•	•
	AEs review [d]	•	•		
	Concomitant medication review	•	•	•	•

a) Only conducted in women of child bearing potential.

b) Nasal swab. Only participants with SARS-CoV-2 antigen negative result, and patients with a history of laboratory-confirmed COVID-19 provided that their CoVID diagnosis is more than 30 days old at the time of enrollment, can be enrolled in the study.

c) In the case that the participant's health condition on the day of enrollment is temporary not suitable for vaccination, he/she is allowed to get the vaccine within a week.

d) All adverse events, whether or not vaccine-related, need to be collected within 21-day post-vaccination.

e) Investigators should complete the "SAE report form" within 24 h after awareness of the event

f) Additional 20 mL of blood is needed to collect from 45 participants in Group A.

g) Demographic only at visit 1

Statistical Analysis	The analysis of safety in this trial is mainly a descriptive analysis of the incidence of adverse reactions/adverse events. A χ^2 test will be used for comparisons between groups (Fisher test will be employed if the assumptions are not met). The neutralizing antibody titers after each vaccine will be analyzed by calculating their geometric means and 95% confidence intervals. A modified one-tail *t*-test will be employed to assess the non-inferiority of the test and reference vaccines for

	exploratory purpose.
Participant Duration	Approximately 6 months

5 INTRODUCTION

5.1 Disease background

Coronaviruses (CoVs) are a large family of viruses that can cause mild to severe respiratory infections in humans. Examples include Middle East Respiratory Syndrome-associated coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV) which caused fatal respiratory illness in 2002 and 2012, respectively. At the end of 2019, a novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China and caused the Coronavirus Disease 2019 (COVID-19)[1].

SARS-CoV-2 is a positive non-segment single-stranded RNA virus, belonging to the Coronaviridae family of Nidovirales. Further phylogenetic analysis showed that SARS-CoV-2 has a closer relationship to SARS virus than to MERS virus[2]. Like other coronaviruses, SARS-CoV-2 can use spike proteins to bind to human lung epithelial cells, interacting with angiotensin-converting enzyme 2 (ACE2) receptor as an entry receptor to the cells. Thereby, the interaction allows viral and cellular membranes to fuse, create immune responses and cause the person to become infected[3,4].

Similarly, to patients with SARS and MERS, cases of COVID-19 often presents as fever, cough, fatigue and chest discomfort. As of 27th July, 2021, there have been more than 194 million confirmed cases of COVID-19, including more than 4 million deaths. The COVID-19 pandemic has brought heavy economic pressure, medical burden, and severe harm to people's lives and health. To date, there are still no specific drugs or therapy approved for COVID-19 that are known to alter the disease course. Therefore, there is an urgent need for effective SARS-CoV-2 vaccines.

5.2 Background of Vaccine

According to the information on the WHO website, there are about 108 candidate vaccines against SARS-CoV-2 under clinical development (including phase 4) and 184 candidate vaccines under pre-clinical development up to date. These candidate vaccines are generally classified into five categories, mRNA vaccines, replicating or non-replicating viral vector based vaccines, DNA vaccines, autologous dendritic cell-based vaccines, and inactivated virus vaccines.

The world's first candidate vaccine against the infection with SARS-CoV-2 was the replication-defective human adenovirus type 5 based COVID-19 vaccine (Ad5-nCoV) that was jointly developed by the Beijing institute of biotechnology and CanSino biologics, which took the lead into the Phase I clinical trial in March 2020. It is demonstrated that Ad5-nCoV exhibited favorable safety profiles and was capable of eliciting both humoral and cellular immune responses. Additionally, a single dose of Ad5-nCoV is able to provide desirable protection against COVID-19 disease caused by SARS-CoV-2. Many countries including but not limited to China, Mexico, Pakistan, Hungary have granted Emergency Use Authorization to this vaccine.

Sputnik V (Gam-COVID-Vac) vaccine was developed by Russian Gamaleya National Centre of Epidemiology and Microbiology. The vaccine is based on two recombinant replication-defective human adenoviruses: Ad26 (serotype 26) and Ad5 (serotype 5). The two adenoviruses are given separately, where

Ad26-S is used in the first dose and Ad5-S is used in the second dose to boost the preventive effect. The vaccine produces protective neutralizing antibody titers against SARS-CoV-2 and creates a strong and durable immunity against COVID-19 according to the clinical trial and real world data[5].

5.3 Background of clinical trials

Phase I and Phase II trials of Ad5-nCoV were carried out in healthy adults aged 18 years and above[6,7]. Both trials showed that vaccination with Ad5-nCoV stimulated robust immune responses in anti-S-RBD antibodies, SARS-CoV-2 neutralizing antibodies, as well as rapid T-cell responses across all dosage levels. To specially point out, the 5×10^{10} VP dosage demonstrated even better safety profiles after vaccination than that of the 1×10^{11} VP dosage but produced a similar immune response. Even though Ad5-nCoV may cause some side effects such as fever, fatigue, muscle pain, or joint pain, most of these adverse reactions are mild and transient.

The pivotal phase III clinical trial to evaluate the efficacy of Ad5-nCoV vaccine is a multi-center, randomized, double-blind, placebo-controlled trial conducted in five countries, Pakistan, Mexico, Russia, Chile, and Argentina. At the time of the interim analysis (cut-off date 10th Jan, 2021), a total of 34,385 subjects were randomized and enrolled, 9.90% of whom are of age 60 years old and above. The vaccine efficacy against all COVID-19 symptomatic disease and severe COVID-19 disease more than 28 days after 1 dose were 65.28% and 90.07%, respectively; efficacy over 14 days post-vaccination in preventing symptomatic and severe disease are 68.83% and 95.47%, respectively.

5.4 Study rationale

Over the past few years, the approach of using different vaccines to prevent several pathogens such as influenza viruses and Ebola viruses, has gained significant momentum against the infection[8,9]. Similarly, some published clinical trials have confirmed that participants who received COVID-19 vaccines using different techniques for prime and boost doses showed stronger immune responses as compared to those who received the same vaccines. In one of our ongoing studies, the sequential administration of Ad5-nCoV following the inactivated vaccine, it was also demonstrated that this prime-boost strategy was capable of eliciting even higher antibody titers against SARS-CoV-2. Therefore, heterologous prime-boost COVID-19 vaccination regimens may be a promising approach to potentiate immune responses and induce a long-lasting immunity.

Sputnik V consists of two different recombinant replication-defective human adenoviruses: Ad26 (serotype 26) and Ad5 (serotype 5) for the two shots[10]. This approach is based on a proven and well-studied platform in Russia, which was successfully applied to an Ebola virus disease vaccine licensed in 2015. Given that the Beijing Institute of Biotechnology and CanSino Biologics Inc. jointly developed Ad5-nCoV using a similar technical route with Sputnik V Ad5-S vaccine, it reasonable that it can act as a candidate to boost Sputnik V Ad26-S. For the purpose of studying the boost effects of Ad5-nCoV on the basis of Ad26-S, the goal of this study is to compare the immunogenicity and safety in subjects that received two doses of the Sputnik V COVID-19 vaccine versus those that received one dose of the Sputnik V plus and a second dose of Ad5-nCoV.

5.5 Risks and benefits

5.5.1 Known potential risks

The safety of Ad5-nCoV vaccine has been proven in the clinical trials in China and abroad. It is very common for people to experience pain, fever, headache, fatigue, myalgia, drowsiness, nausea, and diarrhea after receiving Ad5-nCoV; swelling, itch, redness, induration, joint pain, cough, oropharyngeal pain, vomiting, loss of appetite, dizziness, mucosal disease and pruritus are commonly reported; bleeding, rash, cellulitis, hypoesthesia, gastrointestinal dysfunction, joint swelling, syncope, difficulty breathing, acute bronchospasm, itching (non-vaccination site), acute allergic reaction, skin and mucosa abnormalities are uncommon adverse reactions.

5.5.2 Intended Benefit for Participants

Participants will receive a general health care screening as part of their participation in the study, and these results may be shared with their health care provider. It is possible that vaccination with one dose of Sputnik V plus one dose of Ad5-nCoV may contribute to a better immunity in preventing the infection with SARS-CoV-2. However, the protective efficacy of such regimen is individualized. This study is also beneficial to the entire humanity to fight against SARS-CoV-2.

5.5.3 Risks to the Study Personnel and the Environment

The principle risk to the study personnel is the potential exposure to infectious pathogens in the clinical setting from study participants through various contact mechanisms (e.g., needle stick exposure to blood borne pathogens and exposure to respiratory pathogens). There is also the theoretical risk of vector transmission through exposure to blood or body fluids. Adherence to good hygiene practices and standard operating procedures (SOPs) for working with infectious agents and universal precautions will reduce the risk of exposure.

There are no known risks to the environment other than those associated with the generation of biohazardous waste attendant to vaccination of humans. All biohazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site SOPs.

5.5.4 Assessment of potential risks and benefits

It is a low risk but high return behavior to receive Ad5-nCoV. Close attention will be paid to participant health, especially within the first seven days after vaccination.

6 OBJECTIVES AND ENDPOINTS

6.1 Primary objective

To evaluate the neutralizing antibody titers in subjects that received one dose of the Sputnik V and a second dose of Ad5-nCoV (with an interval of 21-180 days).

6.2 Secondary objective

To evaluate the safety profiles in adults aged 18 years and above that received Ad5-nCoV at least 21 days post-vaccination of one dose of Sputnik V.

6.3 Exploratory objective

To evaluate if the neutralizing antibody titers in participants that received a 1st dose of Sputnik V plus a 2nd dose of Ad5-nCoV is non-inferior to that in participants vaccinated with 2 doses of Sputnik V.

6.4 Endpoints

6.4.1 Primary endpoints

6.4.1.1 Immunogenicity:

The GMTs of SARS-CoV-2 neutralizing antibody on Day 21 post-vaccination of Ad5-nCoV or the 2nd dose of Sputnik V.

6.4.2 Secondary endpoints

6.4.2.1 Immunogenicity

1) The GMT of SARS-CoV-2 neutralizing antibody on Month 3 and Month 6 post-vaccination of Ad5-nCoV or the 2nd dose of Sputnik V.
2) The GMT of S-RBD antibody on Day 21, Month 3, and Month 6 post-vaccination of Ad5-nCoV or the 2nd dose of Sputnik V.

6.4.2.2 Safety

1) The incidence of solicited adverse reactions (ARs) within 7 days post-vaccination of Ad5-nCoV.
2) To evaluate the incidence of unsolicited adverse events (AEs) within 21 days post-vaccination of Ad5-nCoV.
3) The incidence of serious adverse events (SAEs) within 6 months post-vaccination of Ad5-nCoV.

6.4.3 Exploratory endpoints

The GMTs of SARS-CoV-2 neutralizing antibody on Day 21 post-vaccination of Ad5-nCoV and the 2nd dose of Sputnik V.

The SARS-CoV-2 specific T-cell response is studied using flow cytometry, evaluating the expression of activation markers in T CD4+ and CD8+ cells. Expression of CD40L (CD154), and the production of interferon γ (IFN-γ), interleukin-2 (IL-2) and tumoral necrosis factor (TNF-α) will be studied.

7 TRIAL DESIGN

7.1 Overall Design

This is an open-label study to demonstrate the immunogenicity and safety profile in adults aged 18 years and above that received Ad5-nCoV no later than 180 days after the first dose of Sputnik V.

The non-inferiority hypothesis is used for the evaluation of exploratory objective. The ratio of GMTs of SARS-CoV-2 neutralizing antibody in participants on Day 21 post-vaccination of Ad5-nCoV (previously received the 1st dose of Sputnik V) and two doses of Sputnik V is used for the evaluation of this hypothesis. For sample size calculation, the α critical value was set as 2.5% (one-sided comparison); considering 90% power and 10% extra subjects for compensating dropouts, the sample size of Group A (1st dose of Sputnik V plus 2nd dose of Ad5-nCoV) and Group B (2 doses of Sputnik V) was designed to be 450 and 200, respectively.

The study consists of two groups. Participants enrolled in Group A (1st dose of Sputnik V plus 2nd dose of Ad5-nCoV) must have only received the 1st dose of Sputnik V and the interval between the previous injection (1st dose of Sputnik V) and the day of vaccination with Ad5-nCoV should be at least 21 days but no more than 180 days. The comparator data will be obtained from the samples stored at the Immunology Lab of the University of Buenos Aires Medical School, corresponding to subjects who had finished the whole vaccination of Sputnik V. Table 1 shows the group information of this study.

Table 1: Grouping of this study

Group	Cohort	Primary immunization	Regimen	Sample size
Group A	One dose Sputnik V + one dose Ad5-nCoV	1st dose of Sputnik V	≥21 and ≤180días days on the day of enrollment	450
Group B	Two doses of Sputnik V	2 doses of Sputnik V	Stored samples as described above	200
Total	450			

7.2 Scientific rationale for study design

Sputnik V consists of two different recombinant replication-defective human adenoviruses: Ad26 (serotype 26) and Ad5 (serotype 5) for the two shots[10]. This approach is based on a proven and well-studied platform in Russia, which was successfully applied to an Ebola virus disease vaccine licensed in 2015. Given that the Beijing Institute of Biotechnology and CanSino Biologics Inc. jointly developed Ad5-nCoV used a similar technical route with Sputnik V Ad5-S vaccine, it reasonable that it can act as a candidate to boost Sputnik V Ad26-S. For the purpose of studying the boost effects of Ad5-nCoV on the basis of Ad26-S, the goal of this study is to compare the immunogenicity and safety in subjects that received two doses of the Sputnik V

COVID-19 vaccine with those that received a first dose of the Sputnik V plus and a second dose of Ad5-nCoV.

7.3 Study holding rules and safety monitoring

7.3.1 Study suspension criteria

If a suspension criterion is activated, the study will be put on hold, and further injections will not be administered until a safety review has been conducted. Should a suspension criterion be activated, the local PI will inform the IRB, Sponsors, and ANMAT within 24 hours.

Suspension criteria include:

- More than 15% of participants experience a Grade 3 AE beginning within 3 days after study injection (day of injection and 2 subsequent days) and persisting at Grade ≥ 3 on three consecutive days depending upon symptom severity and kinetics·
- A suspected, unexpected serious adverse reaction (SUSAR) occurs that is life-threatening or results in death.

7.3.2 Early termination

The study may come to the early termination, if:

- Required by sponsor, or
- Required by regulatory authority, or
- Required by institutional review board (IRB)

7.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure. The end of the study is defined as the completion of the last visit or procedure for all participants.

7.5 Scheme

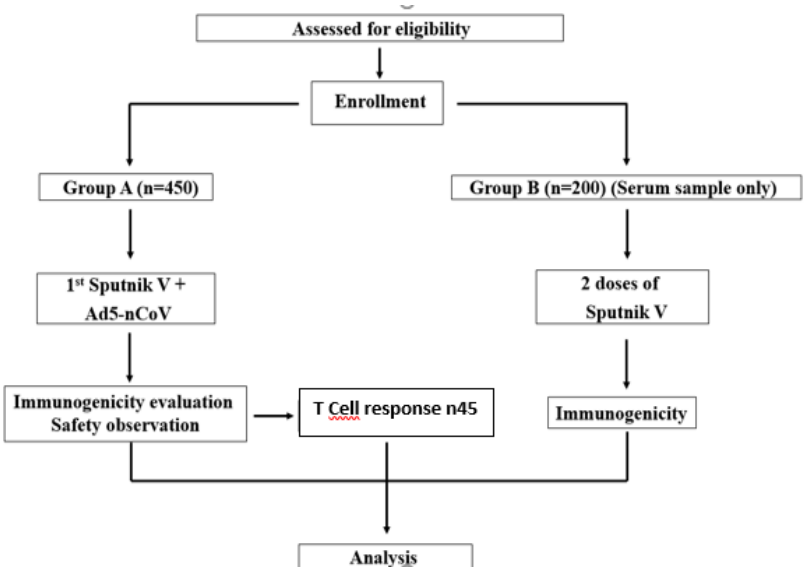

Fig. 1. The flowchart of this study

8 STUDY POPULATION

8.1 Description of study population

Healthy adults aged 18 years and above in Argentina will be informed by a procedure approved by the ethical review committee before consent is sought to be a volunteer. After passing the physical examination and screening according to the following inclusion and exclusion criteria, they will be eligible to participate in this study. Any employee who carries out the research, the relevant researchers, and the members of the contract research organization (CRO) could not be the participants. The following inclusion and exclusion criteria will be used to select the eligible participants for this study.

Group B is a comparator group, in which samples stored corresponding to individuals who have already received 2 doses of Sputnik V will be used for the immunogenicity evaluation.

8.2 Inclusion and exclusion criteria

8.2.1 Inclusion criteria

1. Participants aged 18 years and above at the time of randomization.
2. Provide written informed consent.
3. Axillary temperature ≤ 37℃.
4. Never received any investigational or licensed COVID-19 vaccine other than the 1st dose of Sputnik V with an interval of 21-180 days before the study.
5. Subjects are eligible for immunization of this product as evaluated by investigators after medical history examination, physical examination and clinical judgment of health.

8.2.2 Exclusion criteria

1. Have a history of seizures, epilepsy, encephalopathy, psychosis.
2. History of anaphylaxis to any vaccine component.
3. Positive urine pregnancy test result, pregnant, lactation women, or intend to become pregnant within the next 6 months.
4. Congenital or acquired angioedema/neuroedema.
5. Medical history of Guillain-Barré syndrome.
6. Asplenia or functional absence of spleen.
7. Bleeding disorder (e.g. protein S or factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.
8. Any confirmed or suspected immunosuppressive or immunodeficient state except for HIV infection; received immunosuppressive therapy, cytotoxic therapy, or chronic corticosteroids (excluding corticosteroid spray therapy for allergic rhinitis and surface corticosteroid therapy for acute non-complicated dermatitis) within the past 6 months,
9. History of chronic systematic infection.
10. Administration of immunoglobulins and/or any blood products within the three months prior to the planned administration of the vaccine candidate.
11. Receiving anti-tuberculosis or cancer treatment.
12. History of laboratory-confirmed COVID-19 in the last 30 days, or positive result at the examination of SARS-CoV-2 antigen before vaccination.
13. Planned to receive any vaccine (licensed or investigational), other than the study intervention, within 14 days before and after study vaccination.

14. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban).
15. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, and affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

8.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE are provided.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a specify modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as the initial screening.

8.4 Lost to follow-up procedures/Retention strategies

To maintain contact with the study participants, logbooks, automated email reminders, or computer software capable of ongoing updating and monitoring can be used. If a trial participant fails to appear for a follow-up examination, extensive effort (i.e., at least 3 documented phone calls and/or certified mails) should be undertaken to locate or recall him/her or at least to determine his/her health status. These efforts should be documented in the trial participant's eCRF. Any trial participant who is not available for the final follow-up should be classified as "lost to follow-up" and the classification should be noted on the eCRF together with the reason, if known.

8.5 Withdrawal

8.5.1 Study withdrawal

In accordance with the principles of the current revision of the Declaration of Helsinki, a participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reason(s) for doing so. The Investigator may withdraw the volunteer at any time in the interests of the volunteer's health and well-being:

- Withdraw without any reason
- Administrative decision by the Investigator
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening)

- A major protocol violation that might affect participant's safety or study integrity
- Volunteer non-compliance with study requirements
- An AE, which requires discontinuation of the study or results in inability to continue to comply with study procedures
- Other (specify)

The reason for withdrawal will be recorded in the eCRF. If withdrawal is due to an AE, appropriate follow-up visits or referral for medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilized. Any participant who is withdrawn from the study before vaccination may be replaced, if that is possible within the specified time frame.

Any participant who fails to attend three scheduled follow-up visits with neither communication with the study team nor a clear rationale will be deemed to have withdrawn from the study. If a volunteer withdraws from the study, blood samples collected before his/her withdrawal from the trial will be used/stored unless the volunteer specifically requests otherwise. In all cases of participant withdrawal, excepting those of complete consent withdrawal, long-term safety data collection, including some procedures such as blood sample collection for safety evaluation, will continue as appropriate if participants have received a vaccine dose.

8.5.2 Scope of protocol violation and protocol deviation

Protocol violation list is as follows (including but not limited to):

- Participants does not meet the inclusion criteria or met the exclusion criteria;
- Participants is vaccinated with the wrong vaccine;
- Administration of other vaccine for preventing COVID-19 disease other than Ad5-nCoV and Sputnik V during the study period;
- SAE was not reported within the specified time.

Protocol deviation list is as follows (including but not limited to):

- Beyond the window of vaccination and blood collection;
- Not enough time between other vaccinations, except for emergency (such as rabies etc.).

8.5.3 Procedures for participants with discontinuation

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the investigator to keep the participant in the study. If a participant has to be withdrawn, all efforts will be made to complete and report the trial observations as thoroughly as possible. If a participant needs to be withdrawn, all efforts shall be made to follow safety of the participant as per protocol.

Participants who withdraw prior to vaccination will be replaced. No follow-up of these participants will be performed and no data will be analyzed. Participants withdrawing or withdrawn after vaccination will not be replaced, and their data will be analyzed under the intention-to-treat (ITT) principle.

When a participant withdraws from the study before the planned end of the study period, all investigations scheduled for the end-of-study visit should be performed if the participant agrees. End-of study evaluation will be completed at the time of the participant's withdrawal, with an explanation of the reason for this entered onto the respective "end-of-study" section of the eCRF as follows:

- Adverse event (specify)
- Death
- Protocol violation (specify)
- Medical condition (specify)
- Consent withdrawal, not due to AE
- Other (specify)

9 VACCINE AND IMMUNIZATION PROCEDURES

9.1 Investigational vaccine

9.1.1 Vaccine description

Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector), Ad5-nCoV, is a replication-defective recombinant human type 5 adenovirus expressing novel coronavirus S-protein. It is produced by viral amplification in HEK293SF-3F6 cells, purification and formulation with the addition of proper excipients. The product is used for prevention from infection caused by novel coronavirus.

Active Ingredients: Replication-defective recombinant human type 5 adenovirus expressing S protein of novel coronavirus.

Excipients: Mannitol, sucrose, sodium chloride, magnesium chloride, polysorbate 80, HEPES, and glycerin.

Packaging: The vaccine is contained in a prefilled vial.

Specification: 0.5 mL/ vial (0.4 mL injection is acceptable)

Dosage: 5×10^{10} VP (≥ 4×10^{10} VP)

Shelf Life: 12 months

Storage: This vaccine should be stored and transported at 2-8°C.

Administration: Intramuscular injection in the deltoid muscle of the upper arm.

Schedule: Single-dose schedule.

Manufacturer: CanSino Biologics Inc.
Developers: CanSino Biologics Inc. & Beijing Institute of Biotechnology.

9.1.2 Acquisition and Accountability

The sponsor's representative is responsible for distributing the investigational vaccine to the study site. The sponsor's representative has delegated drug accountability responsibility for this product to the PI; however, the sponsor's representative has ultimate responsibility for product accountability. After the investigational product is released to the study site, the PI is responsible for and will maintain logs of investigational product receipt, storage, reconstitution, accountability by participant, and investigational product remaining before final disposition. At the study site, the logs will be maintained in the accountability files within the regulatory file. The PI may delegate, in writing, this responsibility to another individual, but the PI is ultimately

responsible for the investigational product and its proper storage upon receipt at the study site until it is transferred back to the sponsor's representative or designee, or is destroyed as directed by the sponsor's representative.

All vials (unused, partially used, and spent) will be retained by the study staff for accountability. No vials should be destroyed or disposed without specific instructions from the sponsor's representative and as stipulated by local, state, and federal regulations. This occurs after the study monitor has completed the final accountability inspection. The disposition records will account for all remaining investigational products. The sponsor should provide the full amount of vaccine.

All vaccine packaging must comply with the requirements of clinical trials.

Sponsor is responsible for transportation of the vaccine to the research center, vaccine transportation temperature records (in accordance with the vaccine cold chain temperature) should be submitted along with the experimental vaccine to investigators. The inspection reports (qualified) should be submitted to the sponsor and manager in research center.

To avoid unauthorized access, special area should be used to store and lock the test vaccine. Vaccine is forbidden to inject into anyone except for the participants.

The temperature of the monitoring instrument, transport, and storage of the vaccine should be monitored and recorded twice a day (The site should have an electronic monitoring system with alarm-alert, and manual checks should be done twice a day). Once a temperature deviation happens, where the temperature is beyond the provisions of the 2-8℃ range, the investigators and sponsors should be immediately informed, and the "cold chain damage report form" should be filled. The temperature-deviated vaccine should be identified, placed separately and suspended. Continual usage of vaccines must be written approved by CanSino Biologics Inc. Vaccine out of requirements should be on-site sequestrated.

The test vaccine should be stored in a refrigerator (range 2-8℃) and cold chain equipment should contain a thermometer which records temperature at least every 15 minutes.

Vaccine administrators release the test vaccine to the vaccination staff according to the assigned number of participant and vaccine. The used test vaccine packaging should be recycled after inoculation and detailed records of test vaccine and recycling are needed.

After vaccination, vaccine and packaging will be checked and stored by the administrator. At the end of the study, the researchers will check all the remaining vaccines and packaging.

The total number of vaccines, at any time, unused or damaged, must be consistent with the applicants provided, otherwise, description needs to be provided by the investigator.

9.1.3 Vaccine Storage and Stability

The stability of Ad5-nCoV is currently 12 months at 2-8°C. All movements of the study vaccine will be documented. Vaccine accountability, storage, shipment, and handling will be in accordance with local SOPs.

9.1.4 Measures to avoid introduction in the environment

9.1.4.1 Transfer and storage

The investigational vaccine will be provided to clinical trial center in sealed vials that are appropriately labeled and packaged. The layered packaging ensures containment during transport and is checked for intactness upon arrival. In case of a spill, the site will keep it until the end of the study.

The vials will be stored in refrigerators (2-8℃) at the clinical trial center until use, in an access-controlled area. The amount of vaccines supplied to the clinical trial center is limited to what is needed for the clinical trial. Access to the product is restricted to authorized personnel.

9.1.4.2 Administration

The preparation and administration of the product will be performed by trained personnel, under the responsibility of the investigator, according to a clinical protocol and respecting the rules of Good Clinical Practice.

The primary hazards consist in exposure of mucous membrane or broken skin to droplets or aerosols, and inadvertent parenteral inoculation (injury with needle stick or other sharp objects). Exposure via these pathways can be prevented by application of proper risk management strategies. The clinical trial staff has extensive experience in these manipulations. Gloves will be used for each of these manipulations.

Any contaminated and non-reusable materials will be removed and maintained in sealed containers or in special bags that are further handled as hazardous medical waste in line with the governing legislation. Reusable materials are avoided, but certain equipment, furniture, etc., will remain in the clinical trial center and will be treated with a chemical disinfectant upon completion of the administration.

A study nurse at each clinical site will be responsible for the administration of the IM vaccine into the patient's deltoid muscle. Since this is an open-label study, the study investigators and participants will know the study product they are dispensing or receiving.

9.1.5 Immunization safety precautions and instructions

1) This vaccine is strictly prohibited to be administered by intravascular injection.
2) Epinephrine and other drugs as well as equipment should be in place when the vaccine is used, in case emergency treatment of severe allergic reactions will be needed. Those who are immunized with this vaccine should be observed for at least 20 minutes at the site.
3) As with all vaccines, this vaccine may not produce 100% protection in the vaccinated population.
4) The vaccine must be stored in places not accessible by children.
5) The vaccine should be shaken before injection. It should not be used under following circumstances: presence of foreign objects, cracked vaccine syringe, unclear label or expired, or any other abnormal appearance of the vaccine.
6) No disinfectant in contact with the vaccine when injection.

9.1.6 Contraindications to administration of the product

The following events constitute contraindications to administration of the study products at that point in time. If any contraindication is present at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator.

1) Allergic reaction to any active ingredient, inactive ingredient and substances used in the manufacturing process of Ad5-nCoV vaccine or similar vaccines.
2) History of severe allergic reactions to vaccines in the past (such as acute allergic reactions, angioedema, dyspnea, etc.).
3) Uncontrolled epilepsy and other progressive neurological diseases, and history of Guillain-Barré syndrome.
4) Pregnant and lactating women.

Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the product.

9.2 Other Concomitant Treatment or Vaccines

Concomitant medications/products and concomitant administration

At each participant contact over the phone or in-person, the investigator should question the participant about any medication/product taken and injection received by the participant. Besides, the following prior and concomitant medications/products/vaccines must be recorded in the EDC if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered from 14 days prior to screening up to 21 days following any dose of study product.
- Any concomitant vaccination administered in the period starting from screening up to week 24 after the second dose.
- Prophylactic medication (*i.e.* medication administered in the absence of ANY symptom and in anticipation of a reaction to the injection). *E.g.* an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (only 12 hours before the first vaccination dose).

- Any concomitant medication/product/relevant to MAE and SAE* or administered at any time during the study period for the treatment of a SAE*, or administered at any time during the study for treatment of an adverse event leading to study termination, or treatment of an adverse event requiring a medically attended visit.

**SAEs are required to be reported per protocol.*

Concomitant medications/products/vaccines that may lead to the elimination of a participant from according-to-protocol (ATP) analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the according-to-protocol (ATP) analysis:

- Any investigational or non-registered product (drug or vaccine) other than the study product(s) used during the study period.
- A vaccine not foreseen by the study protocol administered during the period starting from 14 days before injection and ending 14 days after a study vaccine injection. It should be noted that in case an emergency mass vaccination for a unforeseen public health threat other than COVID-19 is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is authorized by the regulatory authority and used according to its package insert and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immuno-suppressants or other immune-modifying drugs administered chronically (*i.e.* more than 14 days) during the study period (for corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent). Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drug administered at any time during the study period (*e.g.* infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

Intercurrent medical conditions that may lead to elimination of a participant from ATP analyses

At each participant contact subsequent to the injection visit, it must be verified if the participant has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Participants may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (*e.g.* confirmed influenza infection) or if they become diagnosed with an immunological disorder.

10 TRIAL METHODS AND PROCEDURES

10.1 Recruitment

Participants will be recruited through invitations to persons in the study center's participant database (who have previously indicated their willingness to be contacted regarding future studies) by mail, social media, e-mail, notification through the study sites' websites, through offices of local physicians, and health care settings. The number of persons who express interest in participating but are ineligible or declined participation, and reasons, will be recorded in the Screening Log.

A subset of 45 participants will be invited to donate extra amount of blood to perform studies on T-cell immunity.

Human peripheral blood mononuclear cells (PBMCs) will be isolated by centrifugation on Ficoll-Paque. After thawing, cells with a viability > 85% will be used. PBMCs will be cultured for 18 h in 96-well U-bottom plates at a density of 1×10^6 to 2×10^6 cells/well and treated with PMA plus Ionomycin (a positive control for T-cell activation), medium only (negative control), or a pool of peptides from the S1 domain of the spike protein. A fraction of the cells will be treated for the last 6 h of the culture with a GolgiStop reagent. Finally,

the activation of CD4+ and CD8+ T cells will be assessed by flow cytometry using antibodies against CD3, CD4, CD8, CD154, IFN-γ, TNF-α, and IL-2.

10.2 Study procedures and interventions

10.2.1 Requirements

In-person visits will take place at selected local study sites in Argentina. The facility will be authorized by the institution to do research related to COVID-19 disease during the pandemic. Scheduling during the pandemic will be arranged to minimize any social contact except with study staff. Study staff will screen potential participants for respiratory or other COVID-19 symptoms over the phone, or WhatsApp and again upon the participant's arrival at the study center. Staff will wear appropriate PPE at all times when interacting with participants to protect the participant and themselves from potential virus transmission in an asymptomatic individual, according to local institutional policies. These institution-wide precautions are meant to minimize the likelihood of a COVID-19 outbreak at the clinical trial site putting participants and staff at-risk, and to preserve the integrity of the study. These procedures will remain in place as long as required by the host institutional policies; study regulations will continue to change to align with the host institution's policies.

10.2.2 Dispensing of investigational vaccine

450 healthy participants aged 18 years and above, who provide consent for participation and fulfil the inclusion criteria and not meet the exclusion criteria will be enrolled in Group A. A subject ID used to identify the participant will be assigned to each individual. According the protocol, participant in Group A will have a subject ID ranging from A001 to A450. Once the subject ID is assigned to a participant, it cannot be reused. The investigator must record the name, date of birth, and subject ID of the participant in the Case Report Form and the EDC system.

Investigational vaccine will be dispensed to participants in Group A. The authorized study staff will be in charge of vaccine administration (IM).

- **Informed consent**
  The signed informed consent (group A) must be obtained before study participation. At each subsequent participant contact requiring an intervention (such as collection of a blood sample), the participant's consent will be verified.
- **Check inclusion and exclusion criteria**
  All inclusion and exclusion criteria will be checked at the screening in-person visit and be reviewed at each subsequent visit.
- **Collect demographic data and contact information**
  Record demographic data such as date of birth, sex, gender, height, weight, and race in the participant's EDC. Current email addresses and/or phone numbers will be collected for each participant. It is important to have complete and accurate contact information for each participant. Contact information may also be used to remind participants of up-coming in-person visits.
- **Medical history**

Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present prior to injection in the EDC. This will include reviewing of any health condition that may prevent the participant from enrolling in the study, such as an unstable health condition or known positive HIV status (with less than 200 CD4 cells/mL).

- **Check contraindications, warnings and precautions to injection**

  Contraindications, warnings and precautions to injection must be checked before vaccination.

- **Urine Pregnancy Test/Birth Control**

  Women of child-bearing age will be asked to perform a urine pregnancy test at the day of enrollment. The result of the urine pregnancy test must be negative. In addition, participants who are able to become pregnant or could impregnate a partner are required to have used approved contraception at least 30 days prior to the study vaccination and for 90 days' post-vaccination.

- **Physical examination**

  The body temperature and blood pressure of all participants needs to be measured prior to any study product administration. Body temperature may be measured by any method (oral, axillary). If the participant has a fever (fever is defined as temperature ≥ 38.0°C orally or axillary) on the day of injection, the injection visit will be rescheduled within 1 week.

  - **COVID-19 history**

    Patients with a history of laboratory-confirmed COVID-19 will not be excluded from the study, provided that the CoVID picture had not occurred within the last 30 days.

- **Screening conclusion**

  Participants will be deemed eligible to participate upon reviewing medical history and inclusion and exclusion criteria. This will occur prior to vaccination.

- **Study group and treatment number allocation**

  The eligible participants will be enrolled into Group A. Each participant will be assigned a treatment identification number (Subject ID). According the protocol, participant in group A will be has a subject ID range from A001 to A450. Once the subject ID is assigned to a participant, the ID cannot be reused. The investigator must record subject ID of the participant in the Case Report Form and EDC system.

- **Check and record prior medications and concomitant medication/injection**

  Prior medications and concomitant medication/injection must be checked and recorded in the EDC. Prior medications should include any medication taken by the participant within 14 days prior to screening. Participants will be asked to avoid over-the-counter medications such as antipyretics (e.g., acetaminophen) and anti-inflammatory medications (e.g., ibuprofen, naproxen) within 12 hours before study vaccine injection but will be allowed to take these kind of medications as needed to treat fever or other adverse events after vaccination. Usage of these over-the-counter medications will be recorded as concomitant medications and linked to the adverse event collected as solicited or unsolicited events according to the symptom.

- **Check and record intercurrent medical conditions**

  Any medical conditions need to be recorded in the EDC.

- **Pre-vaccination serology**

Approximately 10 mL of whole blood will be collected from each participant in Group A at Day 0 and separated for serum. Each serum will be aliquoted into 5 tubes. The first two aliquots will be used to measure for antibodies against SARS-CoV-2 and S-RBD, respectively. The third aliquot will be used for evaluating the base-line HIV antibody if necessary. The results of antibody testing from baseline serum will not be used to determine eligibility for enrollment. All participants will be monitored closely for any SAE and symptoms of illness. The last two aliquots are back-ups.

In addition, approximately 20 mL of whole blood will be collected only in those participants that accept to be part of the cellular immunity sub cohort.

- **Injection of study vaccine**

After completing all prerequisite procedures prior to injection, one dose of the assigned vaccine will be administered IM in the deltoid muscle of the upper arm for participants in Group A. If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within 1 week. There will be a 20 minutes' observation after vaccination to monitor for any adverse reactions.

- **Safety participant contacts**

Participants in group A need to record any AEs they may experience within 21 days post-vaccination. There is an on-site visit on the 21st day post-vaccination and the subjects need to submit their diary card. Participants can report any AEs they experience within 21 days post vaccination. Only SAE will be entered into the EDC during the study period.

- **Following up serology**

All participants in group A will have an in-person visit at Day 21, Month 3, and Month 6 post-vaccination of either Ad5-nCoV. Approximately 10 mL of whole blood will be collected from each participant and separated for serum. The serum will be aliquoted to 5 tubes. The first two aliquots will be used to measure for antibodies against SARS-CoV-2 and S-RBD, respectively. The third aliquot will be used for evaluating the HIV antibody if necessary. The last two aliquots are back-ups.

Approximately 20 mL of whole blood will be collected at pre-specified times only in those participants that accept to be part of the cellular immunity sub cohort.

10.3 Trial schedule

10.3.1 Schedule of Activities (SOA)

There are 4 planned site visits in total,

Intervention	V1	V2	V3	V4
Follow-up time	Day 0	Day 21	Month 3	Month 6

Visit window		+3 days	±10 days	±15 days
Informed Consent	●			
Collect Demographic [g] and Participant Contact Information	●	●	●	●
Physical examination (height, weight, vital signs, body temperature, resting pulse and blood pressure)	●			
Urine Pregnancy test [a]	●			
Check medical history and inclusion and exclusion criteria	●			
SARS-CoV-2 antigen assay [b]	●			
Enrollment [c]	●			
Blood collection [f]	●	●	●	●
Vaccination	●			
Collection of diary/contact card		●		
SAE review [d & e]	●	●	●	●
AEs review [d]	●	●		
Concomitant medication review	●	●	●	●

a) Only conducted in women of child bearing potential.

b) Nasal swab. Only participants with SARS-CoV-2 antigen negative result can be enrolled in the study. Patients with a history of laboratory-confirmed COVID-19 can be enrolled in the study, provided that more than 30 days have elapsed since the diagnosis of CoVID.

c) In the case that the participant's health condition on the day of enrollment is temporary not suitable for vaccination, he/she is allowed to get the vaccine within a week.

d) All adverse events, whether or not vaccine-related, need to be collected within 21-day post-vaccination.

e) Investigators should complete the "SAE report form" within 24 h after the acquisition of the SAE experienced by the participants.

f) Additional 20 mL of blood is needed to collect from 45 participants in Subgroup A.

g) Demographic only at visit 1

Comentado [C1]: COMENTARIO DEL TRADUCTOR:
Traduzco en base a nueva redacción confirmada x mail por Pedro:
Hisopado nasal. Pueden enrolarse en el estudio sólo los participantes con resultado negativo de antígeno del SARS-CoV-2 . Los pacientes con historial de COVID-19 confirmado por laboratorio, pueden enrolarse, siempre que hubieran transcurrido más de 30 días desde el diagnóstico de CoVID.

10.4 **Safety follow-ups**

Only participants in Group A will receive the diary card for monitoring solicited adverse reactions within 21 days post-vaccination. All participants can report SAE at any time during the study.

Part 1: The Diary Card based adverse reaction collecting phase (from day 0 to 7)

After vaccination, each participant in Group A will be asked to stay at study site for at least 20 min safety surveillance. Investigators will monitor the vital signs of the participants and teach them to record any adverse reactions or events on the diary card. If, at that moment, there are no significant adverse reactions, participants will be allowed to go home. At home, participants will record on the diary card axillary temperature and any AEs for 7 consecutive days by their own. There will be an in-person visit on day 21 (Visit 2) for the collection of diary card.

Part 2: In the whole study period from Day 0 to Month 6, SAE will be followed up in a monthly basis and recorded. This will be recorded at each in-person visit and monthly by phone, WhatsApp, or e-mail contact.

10.5 **Unscheduled visits**

Participants may contact the investigator at any time for an unscheduled phone or on site visit should they experience clinical symptoms or signs following injection. At all unscheduled visits the following minimum will be performed:

- Questions concerning the history of the present illness as well as the subject's general health and lifestyle will be asked
- Medically attended AEs and any possible SAEs will be recorded
- Any concomitant medication or vaccination will be noted

After eliciting the history of the present illness and performing any corresponding exams or laboratory tests, the investigator will decide on the best course of treatment according to standard medical practice.

10.6 **Early termination visit**

If the trial is early terminated through specified rules, the investigators will inform the participants.

10.7 **Management of birth control and new pregnancy of trial participants**

Female participants who are pregnant or lactating at the time of vaccination may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or SAE and will be followed-up.

A spontaneous abortion is always considered to be a SAE and will be reported. Furthermore, any SAEs occurring as a result of a post-study pregnancy and considered by the investigator to be reasonably related at the time of receiving the investigational product(s) will be reported to the Sponsor. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

10.8 **Management of specimens**

10.8.1 Specimen preparation, handling, and storage

Samples will be labeled with **subject ID**.

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccine and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by Sponsor outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from Sponsor. Any sample testing will be done in line with the consent of the individual participant.

The blood sample will be isolated for serum, and the isolated serum from each participant will be collected into five sterile tubes which are either test (3 tubes) or backup samples (2 tubes). The former three tubes should contain 0.8 ml and the latter two should not contain less than 0.5 ml, and should be stored in cryogenic refrigerator at -18℃ and below.

10.8.2 Specimen management

Collected samples will be stored for up to 15 years (counting from when the last participant performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the participant consent. These extra requirements need to be communicated formally to and discussed and agreed with Sponsor.

10.9 **Data handling and record keeping**

10.9.1 Confidentiality

Prior to initiation of the trial, the investigators will sign a fully executed confidentiality agreement with the Sponsor. All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by coded number only to maintain participant confidentiality. All computer entries will be done by coded numbers only, and all local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers (or subject ID) to other identifying information will be stored in a separate locked file in an area with limited access.

Sponsor personnel, the IRB and the regulatory authorities will have direct access to source data/documents.

10.9.2 Source documents

The purpose of source documents is to document the existence of the participant and substantiate the integrity of the trial data collected. The Investigator must maintain the trial source documents accurate, complete, legible, and up to date.

Examples of source documents are: participant screening log, laboratory measure reports, enrollment log, participant's diary cards, hospital records, informed consent forms, investigational dispensing, and reconciliation forms, participant's file and records kept at the pharmacy or at the laboratories, mail, and certified letters.

Source data are the data contained in source documents (originals or certified copies). The investigator is responsible for the accuracy and completeness of the data reported in source documents. Data collected by EDC are derived from source documents should be consistent with source documents and any discrepancies should be explained.

All eCRFs in EDC system must have the investigators' electronic signatures. Publishing queries in EDC for incorrect data, then investigators answer the queries to correct the data, or investigators can modify the data directly. The original data will not be removed in EDC; it can be reviewed in the data history records. Other paper documents must be signed by investigators. Incorrect data must be crossed out with single line, initialed and dated. Correction fluid or similar corrective methods that mask the original data will not to be used. Examples are the completion of SAE Reporting Forms, Data Correction Forms, and ICFs.

10.9.3 Case Report Forms

Investigators will use electronic case report forms to collect data in the clinical trial. eCRF is an important part of clinical trials. The data in eCRFs must be clear and intact. Only authorized investigators could correct the errors in the eCRFs or after publishing data queries, investigators will answer the queries to correct the errors. But the original record will not be removed, it can be reviewed in data history records in EDC. The EDC system records when, which data point was modified by investigator and investigator's electronic signature.

According to the project requirements, the data collection, biological sample collection, and examination should be done within the visit window, the original documents and records shall be completed and the results of the examination also should be timely entered into eCRF.

CRA should conduct regular and irregular audits of data records until eCRFs are completed, auditors should carefully verify the number of the participants, data queries and necessary electronic signatures of researchers in EDC system. The main contents of audits should be focused on signed informed consent, volunteer screening into the group, vaccination, management of the investigational vaccine, safety observation and immunogenicity of specimen collection and preservation, Consistency between research data and the original data is the emphasis of audits. Manual verification results will be recorded. For each batch of data, quality control and triggers to computerized logic and/or consistency checks will be systematically applied in order

to detect errors or omissions. Queries will be generated and published in EDC, the investigators will log into EDC to answer the queries.

10.9.4 Participant Diary Card

After vaccination, diary cards will be provided to the participants (ONLY group A) to record any solicited local/general AEs (i.e. on the day of vaccination and during the next 7 days) occurring after vaccination. The participant will be instructed to return the completed diary card to the investigator at the next study visit.

Collection and verification of completed diary card will be carried out during discussion with the participant on Day 21 after vaccination. Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF.

10.9.5 Record retention

Sponsor will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or Sponsor standards/procedures; otherwise, the minimum retention period will default to 15 years.

11 LABORATORY ASSAY AND IMMUNOGENICITY ASSESSMENTS

11.1 General Assessment

11.1.1 Baseline assessment for active participants

Base line is composed of data below.

– Demographics (i.e., name, date of birth, gender, ethnicity/race, weight (kg), height (cm).

–Vital signs of participant, including axillary temperature, resting pulse and blood pressure.

– Pre-vaccination signs or symptoms.

– Underlying or concomitant disease(s).

– Other significant medical history including treatment.

– Previous exposure to the vaccine-specific infectious agent or the vector.

– Any medication taken 14 days prior to and during the baseline assessment

12 SAFETY ASSESSMENT AND MANAGEMENT

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

12.1.2 Solicited AE

Solicited AE are pre-specified and actively monitored for during the trial. Participants are instructed to record solicited local and systemic reactions on a diary card immediately after vaccination, and for the following 7 days.

12.1.3 Unsolicited AE

Unsolicited AE are not specified for active monitoring, but spontaneously reported as untoward events occurring in a participant. Any solicited reaction continuing for > 7 days post-vaccination is additionally captured as an unsolicited AE. Unsolicited AEs leading to premature withdrawal and serious AEs (SAEs) are collected throughout the entire study period.

Investigators are asked to report any unsolicited adverse event in the case report form, independently of possible causal relationship with the vaccines under study. All unsolicited adverse events (AEs) are collected for approximately 21 days after vaccination.

12.1.4 Adverse reaction to immunization (ARI)

Any untoward medical occurrence in a study participant with an established causal relationship to immunization. To be recorded from day 0 to 21 after vaccination

CIOMS/WHO Classification of cause specific reactions:

1. Vaccine product-related reaction: An AE that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

2. Vaccine quality defect-related reaction: An AE that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.

3. Immunization error-related reaction: An AE that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

4. Immunization anxiety-related reaction: An AE arising from anxiety about the immunization.

5. Coincidental event: An AE that is caused by something other than the vaccine product, immunization error or immunization anxiety.

12.1.5 Serious AE (SAE)

A serious AE (SAE) is defined as any event which:

- results in death,
- is life-threatening (i.e., there is risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

In addition, medical and scientific judgment will be exercised in deciding whether other conditions will also be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant's safety or may require intervention to prevent one of the other outcomes listed in the definition above. These will also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.1.6 SUSAR

A SUSAR is defined as an untoward and unintended response to a study vaccine, which is not listed is the applicable product information, and meets one of the following serious criteria:

- results in death
- life-threatening, requires hospitalization
- prolongation of an existing hospitalization
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect Safety data collection

12.1.7 Types of events

12.1.7.1 Solicited AE:

Table 1 lists anticipated local and systemic solicited AEs whose severity are graded according to the FDA published with slight modification. Solicited AEs will be obtained from participant's diary card or clinical visits and recorded to CRF.

Table 1 List of solicited AE and severity grade according to China Guideline from NMPA

Local Reactions (Injection Site)				
Local Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Induration/Swelling	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Erythema/Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Itch	Able to relieve after 48 hours with or without treatment	Unable to relieve after 48 hours with treatment	Prevents daily activity	NA
Cellulitis	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated

Systemic Reactions				
Item	Grade 1	Grade 2	Grade 3	Grade 4
Fever (°C)	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40
(°F)	100.4 – 101.1	101.2 – 102.0	102.1 – 104	> 104
Allergic reactions	Itch without rash	Localized urticaria	Generalized/extensive urticaria, angioedema	Severe allergic reactions
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating /swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Nausea /Vomiting	No interference with activity of 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Joint pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	NA
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	NA

12.1.7.2 Unsolicited AE

In addition to solicited AE that are pre-specified for collection of data, participant should be questioned at each trial visit for the occurrence of any other AEs since the last visit. The investigator also needs to pay attention to other AEs in the diary card fulfilled by participant. The severity of unsolicited AE could be graded according to Guideline from FDA. All unsolicited AE should be treated as solicited AE.

The general grading principles for other adverse reactions (the clinical abnormalities that were not involved in Table 1):

Grade 1 (mild) = Mild, with no interfere with daily activities

Grade 2 (moderate) = Moderate, with a mild interfere with on daily activities

Grade 3 (severe) = Severe, with a significant interfere with daily activities, needs treatment

Grade 4 (Potentially life-threatening) = Emergency or hospitalization

12.1.8 Outcome of events

The adverse reaction / event outcomes include:

- Recovery
- Not yet recovered
- Recovered but with sequelae
- Death

- Loss of follow-up

12.1.9 Documentation

All AE occurring within 21 days following immunization should be recorded in the patient diary card and in the AE report form.

All SAE occurring during the entire trial period starting from the time that each trial participant signs the Informed Consent Form and ending at the last follow-up visit, early termination visit or death, whichever comes first, should be recorded.

12.2 Management of participants with AE

If the participants developed local or systemic adverse reactions or events or serious adverse events, researchers should provide appropriate treatment or medical consultation to reduce or remove suffering. The medical procedures and outcome should be exactly recorded.

12.3 AE reporting

12.3.1 Investigator reporting to sponsor

AE severity grade ≥ 3 or SAE including death due to any cause, which occurs during this study, whether related to the investigational products, must be reported immediately (within 24 hours of the investigator's or assistant of investigator's knowledge of the event) by telephone and E-mail to CROs, principle investigator. Once the CRO receive the notification, it should immediately be transferred to the sponsor.

- A preliminary notification should be made by phone or/and E-mail to the sponsor or agency responsible for reporting and contain the minimal required information:
- Reporter information
- Trial participant's number
- Study vaccine and date of immunization
- Description of the event which to enable CRO to file a report that satisfies regulatory reporting requirements.
- Severity
- Investigator's causality assessment

In addition to the initial 24-hour report (notification), a completed, separate SAE report is to be sent to CRO via email or mail within 48 hours of the event. The final SUSAR report will be provided after evaluation of the sponsor. All SAEs will be recorded in the safety screen of eCRF and source documents. Please contact with Medical Monitor Maria Ines Figueroa (E-mail: uam@huesped.org.ar) for SAE and SUSAR report.

12.3.2 Reporting to regulatory authorities

12.3.2.1 Reporting of SUSARs to the competent authority

The sponsor of a clinical trial conducted in Argentina should notify each SUSAR within days:

- *Life-threatening or fatal events (≤ 7 days)*
- *Other events (≤ 15 days).*

The SUSARs should be sent in the ICH E2B format to the ANMAT. Additional questions relating to reporting can be sent to Medical Monitor Maria Ines Figueroa (E-mail: uam@huesped.org.ar).

12.3.2.2 Reporting of SUSARs to the Ethics Committee issuing the single opinion

The sponsor of a clinical trial conducted in Argentina should report each SUSAR occurring in clinical trial concerned to the Ethics Committee issuing the single opinion within 14 days.

The format for submission to the Ethics Committee issuing the single opinion is not defined. Electronic submission is possible but should be accepted in advance by the relevant Ethics Committee.

12.3.3 Reporting of follow-up information

Any relevant information concerning a SAE that becomes available after the initial SAE report form has been sent should be forwarded to the sponsor within 24 h.

Any post-trial event may also be reported by the investigator to the sponsor. Such report should be regarded as a trial report and will require causality assessment by the investigator.

12.4 Assessment of causal relationship

Investigators adopt causal assessment method of WHO system [Causality Assessment of an adverse event following immunization (AE) 2nd edition].

The cause-specific classification proposed by the WHO is shown in **Table** 2.

Table 2 Classification in assessing causal relationship

Levels	Definition
Very likely /certain	Clinical event with a proximal, biologically plausible, time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	Clinical event with a relatively brief interval between vaccination and the event and which unlikely to be attributed to concurrent disease or other drugs or chemicals
Possible	Clinical event with a relatively brief interval between vaccination and the event but which could also be explained by concurrent disease or other drugs or chemicals
Unlikely	Clinical event with a time relationship to vaccine administration that makes causal connection improbable but which could plausibly be explained by underlying disease or other drugs or chemicals

Unrelated	Clinical event with a biologically incompatible time relationship to vaccine administration and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	Clinical event with insufficient information to permit assessment and identification of the cause

For solicited AE considered to be routine reactogenicity captured in diaries (e.g. solicited injection site reactions within 7 days post-vaccination, fever within 7 days post-vaccination, etc.) specific causality assessments are not performed.

13 TRIAL MONITORING

13.1 Overall monitoring plan

Study monitoring will be conducted in accordance with relevant SOPs and local regulations. A confirmation letter will be sent to the site prior to each visit. Following each visit the CRA will complete the appropriate monitoring report. Items of note found during an interim a monitoring will be discussed with the Principal Investigator (PI) and/or appropriate staff (e.g. sub-investigator, study coordinator) and included in the monitoring report with resolution documented. A follow-up (FU) letter should be sent to the PI after the visit within the five working days after the visit summarizing activities held during the visit, resolution of previously noted actions items and any outstanding or new issues requiring resolution.

Regarding the frequency of Monitoring Visit, following trial site initiation, the first ongoing monitoring visit should occur within two (2) working days after the first subject included into study is enrolled.

Routine Monitoring visits will be scheduled at least every 4 weeks.

Unscheduled Visit will be conducted if the site emerges continuous major PD or any other significant event (e.g. SAEs, Misconduct, Serious Breach, etc).

The final last routine monitoring visit should be conducted prior to the database lock.

The close out visit will be performed after the date base lock unless the site is terminated earlier due to non-performance or any other reason approved by the Sponsor.

Remote monitoring and SDV carried out by monitor at a location other than the sites at which clinical investigation is being conducted is allowed in order to encourage less emphasize on on- site monitoring during this pandemic period, as an exceptional situation. There are different methods of how the remote monitoring may be carried out. It may involve remote SDV by site staff uploading the source documents to a secured and encrypted portal abide to country privacy law and 21 CFR part 11 (if applicable) or use of technology (i.e. teleconference meeting that enables monitor to verify the data remotely. Whichever the method chosen by site is, the security of the platform should be carefully assessed, and the monitoring method should be accepted / approved by the ethics committee and / or local authority, as applicable. The recommended source document platform to use would be: Veeva SiteVault free. The system validation information of the Veeva SiteVault free platform is available

here: *https://sites.veevavault.help/gr/validation_docs/*. The account is fully owned and controlled by site staff and they are responsible to grant access to the monitor who will be monitoring at their sites.

14 DATA MANAGEMENT

14.1 Source documents and source data

14.1.1 Source documents

The purpose of source documents is to record the existence of the participants and substantiate the integrity of the trial data collected. The Investigator must maintain the trial source documents accurate, complete, legible, and up to date.

Examples of source documents are: participant screening logs, laboratory measure reports, enrolment log, participant's diary cards, hospital records, informed consent forms, investigational dispensing and reconciliation forms, participant's file and records kept at the pharmacy or at the laboratories, mail, and certified letters.

14.1.2 Source data

Source data are the data contained in source documents (originals or certified copies). The investigator is responsible for the accuracy and completeness of the data reported in source documents. In this trial EDC (electronic data capture) is used for collection of clinical data. All the data in EDC system is derived from source documents should be consistent with source documents and any discrepancies should be explained. Investigators must do electronic signature for data in EDC system.

For paper documents. Incorrect data must be crossed-out with a single line, then initialed and dated. Correction fluid or similar corrective methods that mask the original data will not to be used. These rules also apply to the completion of SAE Reporting Forms, and ICFs.

Monitoring plan:

Regarding the frequency of Monitoring Visit, following trial site initiation, the first ongoing monitoring visit should occur within two (2) working days after the first subject is enrolled into study.

Routine Monitoring visit will be scheduled at least every 4 weeks.

Unscheduled Visit will be conducted if the site emerges continuous major PD.

The final monitoring visit should be conducted prior to the database lock.

The close out visit will be performed after the date base lock unless the site is terminated earlier due to non-performance.

Remote monitoring and SDV carried out by monitor at location other than the sites at which clinical investigation is being conducted is allowed in order to encourage less emphasize on on-site monitoring during this pandemic period. There are different methods of how the remote monitoring may be carried out. It may involve remote SDV by site staff uploading the source documents to a secured and encrypted portal abide to country privacy law and 21 CFR part 11 or use of technology i.e. teleconference meeting that enable monitor to verify the data remotely. Whichever method chosen by site, the security of the platform should be carefully assessed, and the monitoring method should be approved by the local authority, as applicable. The recommended source document platform to use would be: Veeva SiteVault free. The system validation information of the Veeva SiteVault free platform is available here: *https://sites.veevavault.help/gr/validation_docs/*. The account is fully owned and controlled by site staff and they are responsible to grant access to the monitor who will be monitoring at their sites.

Further details about the monitoring activities are described in the Monitoring Plan.

14.2 Clinical data management and responsibilities

The investigators\CRCs should do data entry in EDC system. EDC is used to collect data in clinical trials, the data in EDC should be clear, accurate and intact. Only authorized Investigators\CRCs answer the queries from CRA, DM, and EDC system (The queries generated according to Edit Checks). After a query is answered, the data is updated, but the initial data is still stored in EDC system and can be reviewed.

According to the project requirements, the data collection, biological sample collection and examination should be done within the visit window, the original documents and records shall be complete and the results of the examination also should be timely entered into EDC.

Auditors should conduct regular and irregular audits of data records until all the eCRFs are completed, auditors should carefully verify the participants' numbers, the data in each eCRF and electronic signatures of investigators. The main contents of audits should be focused on signed informed consent, volunteer screening into the group, vaccination, management of the investigational vaccine, safety observation and immunogenicity of specimen collection and preservation, Consistency between data in EDC and the original data is the emphasis of audits.

14.3 eCRF design and data entry

14.3.1 eCRF design

EDC admin is responsible for eCRF design. eCRF design include electronic tables and Edit Checks.

- Electronic tables for data collection.
- Edit Checks to do data validation when investigators\CRCs are doing data entry.

14.3.2 Data entry

The investigators\CRCs should perform data entry in EDC system, and answer the queries. The queries are published by CRA, DM, and EDC system (The queries generated according to Edit Checks). After a query

was answered, the data is updated, but the initial data is still stored in EDC system and can be reviewed. When all the queries in the EDC system were answered by investigators, the data should be frozen and data entry will be finished.

14.4 Data review and lock

Review of the data is required before Statistical analysis. The aim of data review is to determine the population that will be analyzed according the evaluation criteria, including full analysis set (FAS) under the principle of ITT (intention-to-treat analysis), per-protocol set (PPS) and safety analyzes datasets, confirmation of the deviation from the project and other influences on database. If there is no more problem of data in EDC, data will be locked after the review.

15 STATISTICAL CONSIDERATIONS

After the last subject has completed all the required visits, database entry is completed, data blind review is finished and database is locked, the final analysis will be done by the trial statistician.

The statistical analysis of this trial will be performed as described and summarized in the protocol. Full details of the planned statistical analyses will be described in the statistical analysis plan (SAP). Test statistics and the corresponding *p*-values will be given.

15.1 Statistical Hypotheses for exploratory objective

Null hypothesis (**H0**)：*Lower bound of 9*5% CI of $GMT_A/GMT_B \leq \Delta$

Alternative hypothesis (**H_1**)：*Lower bound of 95% CI of* $GMT_A/GMT_B > \Delta$

The non-inferiority boundary was chosen as Δ = **0.5**. GMT_A means GMT of Group A (1st dose of Sputnik V plus Ad5-nCoV) and GMT_B means GMT of Group B (2 doses of Sputnik V). The ratio of Geometric mean titers (GMTs) of SARS-CoV-2 neutralizing antibody in participants who previously received the 1st dose of Sputnik V on Day 21 post-vaccination of Ad5-nCoV and the second dose of Sputnik V is used for the evaluation of this hypothesis. The type I error is set as 2.5%.

15.2 Statistical Plan

15.2.1 Sample Size Determination

For the calculations, the α critical value was set as 2.5% (one-sided comparison) and power at 90%. If the neutralizing antibody test/reference ratio = 1 with a non-inferiority margin of 0.5 (setting the standard

deviation to be 0.63), it is assumed to enroll about 100 subjects for each group. Additionally, 45 participants will be selected from Group A (to enter the immunogenicity subgroup for cellular immune response analysis. According to the above, considering extra subjects for compensating about 10% dropouts, the sample size of Group A is designed to be 450, for Group B is 200.

15.3 Data set for Analyses

15.3.1 Data set for safety evaluation

Safety evaluation data set (SS): All subjects who received vaccination after randomization should undergo safety evaluation. Data that violated the protocol should not be eliminated.

15.3.2 Data set for immunogenicity evaluation

Immunogenicity evaluation data set:

Full analysis data set (FAS): FAS is an ideal subject population determined according to the principle of ITT (intentional analysis). All subjects enrolled and vaccinated are included in the FAS set, regardless of whether they have a positive baseline HIV antibody level or not. Seriously violated the test plan.

Comentado [C2]: COMENTARIO DEL TRADUCTOR: ESTA FRASE PARECE DESCOLGADA

Per protocol set (PPS): It is a subset of FAS. Subjects in this data set are more compliant with the plan, have no major violations of the protocol during the study period, and all meet the inclusion/exclusion criteria.

In this experiment, the per protocol set (PPS) will be used as the main analysis set. However, FAS must be analyzed at the same time. Any inconsistency between FAS and PPS analysis results must be discussed in the report.

15.4 Statistical Analyses

15.4.1 General Approach

In the process of statistical analysis, firstly check the number of completed cases and the dropouts; then analyze the demographics and baseline characteristics of each group of cases at the time of selection to examine the comparability between groups; the evaluation of vaccine effects includes the determination of evaluation endpoints, and comparison of effects between groups; safety evaluation includes statistics of clinical adverse reactions/events.

Criteria for excluded cases: those who do not meet the criteria for selected cases; those who fail to follow up with data and information after vaccination; those who have severely missing information and data after randomization; the subject meets the criteria for withdrawal but did not withdraw; the subject accepts wrong vaccination or incorrect dose.

The analysis of safety in this trial is mainly a descriptive analysis of the incidence of adverse reactions/adverse events. The χ^2 test will be used for comparison between groups, and Fisher's exact test would be used if necessary. In immunogenicity analysis, antibody level requires logarithmic transformation, which should be expressed in terms of GMT, standard deviation, median, maximum and minimum, and 95% confidence interval. Comparison of classification indexes between groups, such as antibody positive conversion rate χ^2 test was used, and Fisher's exact test would be used when necessary.

The neutralizing antibody titers after each vaccine will be analyzed by calculating their geometric means and 95% confidence intervals. A modified one-tail *t*-test will be employed to assess the non-inferiority of the test and reference vaccines.

In a subset of 45 participants, T-cell response will be assessed in vaccinated individuals using the COVID-T platform. This strategy involves purification of peripheral blood mononuclear cells (PBMC) from whole blood of vaccinated individuals, culture with specific peptides (S-S1/N-M) derived from SARS-CoV-2 Spike protein at different time periods and further analysis of cell surface markers and intracellular cytokines by flow cytometry. These data is finally integrated into an activation co-efficient using appropriate negative and positive controls of T-cell activation. This will be studied at day 0, day 21, month 3, and month 6 post-vaccination

15.4.2 Safety analysis methods

Adverse events will be coded using the MedDRA dictionary. The analysis of adverse events will be based on treatment emergent adverse events (TEAE) that occurred after vaccination. TEAE is defined as an adverse event that occurs during vaccination or worsens during vaccination compared to before vaccination. The incidence of TEAE will be described in terms of system organ classification (SOC) and preferred term (PT). At the same time, a similar summary and list of serious adverse events (SAEs) and adverse events that led to the discontinuation of the study are provided.

1. The incidence of solicited ARs within 7 days post-vaccination of Ad5-nCoV.
2. To evaluate the incidence of unsolicited adverse events (AEs) within 21 days post-vaccination of Ad5-nCoV.
3. The incidence of serious adverse events (SAEs) within 6 months post-vaccination of Ad5-nCoV.

15.4.3 Immunogenicity analysis methods

1. The GMTs of SARS-CoV-2 neutralizing antibody on Day 21, Month 3, and Month 6 post-vaccination of Ad5-nCoV.
2. The GMTs of S-RBD antibody on Day 21, Month 3, and Month 6 post-vaccination of Ad5-nCoV.

15.4.4 Exploratory analysis

1. The GMTs of SARS-CoV-2 neutralizing antibody on Day 21 post-vaccination of Ad5-nCoV and the 2nd dose of Sputnik V.
2. The SARS-CoV-2 specific T-cell response is studied using flow cytometry, evaluating the expression of activation markers in T CD4+ and CD8+ cells. Expression of CD40L (CD154), and the

production of interferon γ (IFN-γ), interleukin-2 (IL-2) and tumoral necrosis factor (TNF-α) will be studied.

15.4.5 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized overall and then by treatment group using appropriate descriptive statistics. Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using frequency counts and percentages. 95% confidence intervals will be reported, but no statistical hypothesis testing will be conducted. Results will be presented for all participants.

The demographic data include: enrollment and completion of the visit (screening failure, plan violation); the number of people entering each data set and the age and gender distribution of each group.

Baseline characteristics include: antibody distribution of each group and total immunogenicity evaluation before immunity.

15.4.6 Analysis arrangement

1. The first staged statistical analysis will be conducted after the completion of reviewing the safety and immunogenicity data 21 days post-vaccination of Ad5-nCoV.
2. The final statistical analysis will be conducted after finishing all the safety and immunogenicity evaluation as per protocol.

16 QUALITY ASSURANCE

16.1 Quality control of investigational vaccine

Investigational vaccines should be managed specifically. The vaccine management and recording system should be available from sponsor to investigator and accept the supervision of the monitor. The number of vaccines, people vaccinated, remaining quantities, and the received amount of damage need to be recorded in the work log.

The sponsor will send the investigational vaccines to the investigators site via qualified shipping company. In this study, if the investigators find any damages of the vaccine or the bulk material cannot be shaken to dissolve, the investigational vaccines will be restored without use. If the transportation and preservation process in cold chain system is damaged, the vaccine should not be used. They should be separately stored and clearly marked and returned to the sponsor by the responsible person for management. Investigators must sign the vaccine transfer receipt to confirm all vaccines received, the receipt shall be stated briefly the information of received vaccine including the amount, the package, and the cold chain system.

At the end of the study, the researchers will check all the remaining vaccine and package and deliver them back to sponsors. The total number of used, unused, or damaged vaccines must be documented and be consistent with the applicants provided. Otherwise, the investigators must provide a description.

16.2 Trial/data auditing

16.2.1 Original files

Original data includes the participants' demographic data, inquiry results of medical history, examination results, laboratory test results, vaccine immunization records, records of bleed, combined medication and adverse events / reaction and treatment and outcome etc. All information shall be recorded in the original medical records and kept in a special room. The original data will be archived in the research center, and it is the basis of data authenticity and integrity.

Visit recording and other original records should be carefully, accurately and immediately filled by investigators. All the raw data should be collected in the record of inoculation and visit. The raw records include the following basic data:

- Items of experiments, participants' number, random coding of participants
- Demographic data
- Inclusion / exclusion criteria
- Physical examination results
- Laboratory test results (including Immunology)
- Vaccination record
- The date of the visit and the date of termination of clinical trial
- Adverse events /reactions and their treatment and outcome
- Blood collection record
- Concomitant drug treatment, medical treatment and other vaccination

16.2.2 eCRF

The data of eCRFs for every participant is saved in the EDC system. Sponsors and investigators have rights to review and download the data in the EDC system. Only investigators and approved staffs have rights to log in the EDC system. During the trial, the participants complete the research or withdraw, investigators must review the data of participants in the EDC system and submitted the electronic signatures on eCRFs of accurate data. The cause of the early termination should be recorded in eCRFs.

The situation of each stage of the participants should be reflected in eCRFs during the trial. Names of the participants cannot be shown in eCRFs or any other parts in EDC system, the appropriate code or the names in initials could be used. All the data on the eCRFs comes from the raw data and will be consistent with the original data. All the data recorded in the eCRFs should be recorded in the original data.

16.2.3 Storage of files

Written documents should be issued after modified by the sponsors, investigators, and other relevant parts about clinical trials meetings, protocol, informed consent, and all the original data. All their agreement documents will be copied in two files and saved respectively. All files or their copies related to the clinical trial will be handed over to the Sponsors.

Preservation of clinical trial data must be accorded to GCP. Investigators should save data at least 5 years more than the end of clinical trials while the clinical trial data should be permanently preserved by sponsors.

16.2.4 Quality control of biological sample

Serum samples for antibody detection should be collected within 5 hours after centrifugation with a hemolysis rate of serum less than 2% and the error rate less than 1%.

The serum samples used for other detection are collected, processed and preserved in strict accordance with the requirements of SOPs.

16.3 Procedure for protocol modifications

No changes to the study protocol will be allowed unless approved by the sponsors. This does not apply to changes made to reduce discomfort or avert risk to study participants. Furthermore, in the event of a medical emergency, the investigators shall perform any medical procedures that are deemed medically appropriate. The principle investigator must notify the sponsor of all such occurrences.

Written IRB approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRB for information only. Any amendment/administrative change to the protocol will be adhered to by the participating center(s) and will apply to all participants. Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. When submission to the local regulatory authority is required, the timing of the submission relative to IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

17 ETHICAL CONSIDERATIONS

17.1 Declaration of Helsinki

Study investigators will ensure that this study is conducted according to the principles of the latest revision of the Declaration of Helsinki (Fortaleza, Brazil, October 2013).

17.2 ICH Guidelines for Good Clinical Practice (GCP)

Study investigators will ensure that this study is conducted in full conformity with the ICH Good Clinical Practice (GCP) and local regulatory requirements.

17.3 Ethical review

The investigator is responsible for obtaining written approval for the clinical study protocol (including all substantial protocol amendments), the written participant informed consent form, informed consent updates, participant recruitment procedures (e.g. advertisements), and any other written information to be provided to

participants from an IRB which complies with local regulatory requirements. Any amendments will require approval by the IRB.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the Institutional Review Board and the sponsor in writing immediately after the implementation.

A final study notification will be forwarded by the investigator to the IRB within 90 days after the study has been completed or in the event of premature termination of the study within 15 days. Copies of all clinical study status reports (including termination) will be provided by an investigator to CRO.

17.4 **Informed consent**

Sponsor will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and Sponsor required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgment, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to Sponsor and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

17.5 **Benefits and risks to the participant**

Benefits to the participant include the additional medical attention she or he will receive, with baseline and regular physical checks, urine test (women of childbearing age only), HIV test, COVID-19 test, as well as the satisfaction that may result from taking part in a project that could potentially lead to the protection of many people from an untreatable and often fatal illness.

The risks to the participant are the potential side effects of the vaccine, as described above in Section 4.6.1, as well as the pain and bruising that may occur as a result of the blood draws described above.

17.6 **Confidentiality**

The sponsor, investigators, ethics committee (IEC) or representatives of full authorized management such as EMA、NMPA have the right to access the clinical trial data, but the relevant content cannot be used for any other clinical trials or disclosed to any other person or entity.

A confidentiality agreement must be signed by the investigators to verify their awareness and agreement with the information in this research is kept confidential.

The investigators and other researchers should keep all the information provided by the sponsors and all the data / information generated in the research center (except the medical records of the participants) confidential. This information and data cannot be used for any other purpose out of this study. This restriction does not apply to: (1) research information is publicly but not due to the violation of investigators and researchers; (2) public the research information to the IRB / IEC for the purpose of evaluation; (3) to provide proper medical assistance lead to information disclosure; or (4) research results published after sponsor authorized. If the written contract confidentiality terms of this study should be offset with this statement, processed by prevail of this statement.

17.7 Conflict of interest of investigator

The investigator acts as chief and principal investigator for vaccine trials conducted on behalf of Fundacion Huesped. CanSino Biologics Inc. grants the use of Ad5-nCoV.

18 PUBLICATION AND DATA SHARING POLICY

18.1 Publication and data sharing policy

This study will be conducted in accordance with the following publication and data sharing policies and regulation of ANMAT (Argentine National Administration of Drugs, Foods and Medical Technology). This trial will be registered on ClinicalTrials.gov.

18.2 Conflict of Interest Policy

The ANMAT (National Administration of Drugs, Foods and Medical Technology) takes care to ensure that its scientific experts, staff, and Management Board do not have any financial or other interests that could affect their impartiality. The Agency has separate policies in place for these groups. This study will be conducted in accordance with the Agency's policy on the handling of competing interests of scientific committee members and experts and handling competing interests for Management Board members and breach-of-trust procedure.

18.3 Additional Considerations

All data / information generated in the research center (except the medical records of the participants) belong to sponsors and CanSino biologics Inc. If the written contract confidentiality terms of this study should be offset with this statement, processed by prevail of this statement.

Before the research results in submission, speaking, teaching or other form of public (collectively referred to as "publication"), a content copy must be submitted to sponsors to obtain written approval, and the results can be published. The confidential information and personal information of the participants (such as the name or initials) cannot be included in research results.

19 FINANCING AND INSURANCE

19.1 Compensation to trial participants.

Patient will be reimbursed for reasonable expenses regarding surface transportation, which will be offered by the research sites. All study visits and related assays will be financed by the study, with no charge to the participants or their healthcare insurance carriers.

19.2 Insurance for trial participants

An agreement will be signed by all the parties involved in the trial's performance, if relevant. Adequate insurance coverage for all participants to be included in the trial is supplied by the Sponsor.