CLINICAL RESEARCH & IMPACT EVALUATION DIVISION

CLINICAL TRIAL FINAL REPORT

STUDY TITLE

"Exploratory study of the SOBERANA® Plus ST vaccine, to evaluate its reactogenicity and immunogenicity in adults from Italy: convalescents from COVID-19, and in subjects with no history of this disease previously immunized against SARS-CoV-2"

SOBERANA PLUS TURIN

IFV/COR/16

RPCEC 00000397

July 2022

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1 SYNOPSIS

An exploratory study of the SOBERANA® Plus ST vaccine, prospective, open, uncontrolled, in parallel groups and multicenter (Cuba and Italy), was carried out to evaluate the reactogenicity and immunogenicity of a dose of this vaccine in adults from Italy.

1.1 General Objective:

To assess reactogenicity and immunogenicity of the SOBERANA® Plus ST vaccine against SARS-CoV-2 in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS-CoV-2.

1.2 Specific Objectives:

1. To evaluate the reactogenicity of a dose of SOBERANA® Plus ST in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS-CoV-2.
2. To evaluate the immunogenicity of a dose of SOBERANA® Plus ST in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS-CoV-2.

Population: Two groups were planned, each with up to 30 volunteers. The first would be made up of convalescents from Italy with a history of mild or moderate clinical symptoms of COVID-19. Adults, of any sex, between the ages of 19-59, who gave their consent to participate and who met the selection criteria. The second by volunteers from Italy, healthy, of either sex, between the ages of 19-59, with no history of having suffered from COVID-19 and vaccinated against SARS-CoV-2, who also gave their consent. of participation and that they met the selection criteria. During the pre-recruitment carried out in Italy, and the recruitment carried out in Cuba, the volunteers of the convalescent group were excluded, so the study was limited to the second group, made up of volunteers previously immunized with other SARS-CoV-2 vaccines.

Treatment: One dose of SOBERANA® Plus ST (50 µg of d-RBD adjuvanted in aluminum hydroxide gel).

Overview: Adverse events were assessed during one hour of post-immunization observation at the clinical site followed by active and passive surveillance with outpatient follow-up for up to 28 days. Immunogenicity was studied by determining the levels of specific anti-RBD IgG antibodies and the in

vitro inhibition of RBD binding to its ACE2 receptor, including the determination of inhibitory titers (IT) 50 techniques carried out in Cuba, and viral neutralization against the D614G, beta, delta and omicron variants, at the “Amedeo di Savoia” Hospital, in Italy, and at the Cuban Civil Defense Laboratory. The immune response detected before vaccination with SOBERANA® Plus ST was compared with that achieved 28 days after vaccination.

Primary endpoint: This study explored the reactogenicity and immunogenicity of SOBERANA® Plus ST in the populations evaluated. “Satisfactory Immune Response” was not defined.

Most important results: During this study, the Investigational Product was shown to be safe and well tolerated. Adverse events related to vaccination were few (37% of subjects), all mild, predominantly pain at the vaccination site. All the immunological variables evaluated increased significantly after vaccination: anti-RBD antibody concentration, in vitro inhibition of RBD:ACE2 interaction, TI50, and in vivo neutralization test. To highlight the neutralizing response induced by the vaccine against all the variants of SARS-CoV-2 evaluated.

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2 LIST OF ABBREVIATIONS AND TERMS DEFINITIONS

Ac/Ab: Anticuerpo/Antibody.

Ag: Antígeno/Antigen.

Al: Alúmina/Aluminum.

BPC/GCP: Buenas Prácticas Clínicas/Good Clinical Practices.

BPM/GMP: Buenas Prácticas de Manufactura/Good Manufacturing Practices.

CECMED: Centro para el Control Estatal de la Calidad de los Medicamentos, Equipos y Dispositivos Médicos. (Cuban Regulatory Agency for Drugs, Medical Equipment and Devices)

CEI: Comité de Ética de las Investigaciones / (Investigations' Ethics Committee)

CENCEC: Centro Nacional Coordinador de Ensayos Clínicos/ (National Coordinating Center for Clinical Trials)

CIMD: Comité Independiente de Monitoreo de Datos. / (Data-handling Independent Committee)

Consulta NO presencial/ Non-face-to-face consultation: For the purposes of this Protocol, we define it as a non-physical consultation, available for the convalescent in case of any eventuality; the subject may call to the phone numbers appearing in the "Information Sheet for the Subject" and in the "Identification Card", as well as through other numbers and ways (for example, by e-mail) the researches provide, so the subject can report any adverse event, or for dealing with any concern.

The researcher might ask the volunteer to contact the research team during determined days after vaccination, to learn about his/her health condition. On the other hand, even when during certain periods, there are not face-to-face consultations established, there will be a consultation office available in the clinical sites, to which the volunteer can always go.

COVID-19, mild: Disease caused by the SARS-CoV-2 coronavirus. Defined as mild, when it presents non-specific signs and symptoms, such as loss of taste and smell, fever, cough, sore throat, nasal congestion, slight headache, general discomfort, and digestive manifestations (nauseas, vomits and diarrheas), without dehydration, dyspnea, or sepsis; a picture virtually indistinguishable from other respiratory viral conditions.

COVID-19, moderate: When in addition to the above signs and symptoms, the patient presents intense cough that may be productive, polypnea, with cracking rales, or it can appear as an atypical pneumonia, although without signs of respiratory insufficiency or seriousness. It classifies as a moderate clinical picture, when these patients, as well as the ones classified as mild, have not required hospitalization in intensive care units.

CRD: Cuaderno de Recogida de Datos/ Data Collection Notebook.

d-RBD: RBD Dimer: Receptor-Binding Domain of the SARS-CoV-2 virus.

EAS/RAE: Evento Adverso Solicitado/Solicited Adverse Event.

EAE/EAE: Evento Adverso Esperado/ Expected Adverse Event.

EAG/SAE: Evento Adverso Grave/ Serious Adverse Event.

EAGI/SUAE: Evento Adverso Grave e Inesperado/ Serious and Unexpected Adverse Event

EANE/NEAE: Evento Adverso No Esperado/ Non-Expected Adverse Event

ELISA: Análisis de Inmunoabsorción Ligado a Enzima/ Enzyme- Linked Immunosorbent Assay.

IFV: Instituto Finlay de Vacunas/Finlay Vaccine Insitute

INM/IMM: Inmunógeno/ Immunogen

MGI/CGM: Medicina General e Integral/Comprehensive General Medicine

OMS/WHO: Organización Mundial de la Salud/ World Health Organization

PCR: Reacción en Cadena a la Polimerasa / Polymerase Chain Reaction. In this study we will refer to PCR for SARS-CoV-2 diagnosis

SNS: Sistema Nacional de Salud/ National Health System

Título Inhibitorio 50/ Inhibitory Titer 50 (TI50): Measurement indicating the quantity of antibodies (titer) required for *in vitro* inhibiting the interaction between the RBD and its ACE2 receptor in a 50%. Identified in this study also by its Englsh acronym mVNT50 (molecular viral neutralization titer 50).

Test Rápido de Antígenos (TRA)/ Rapid Antigen Test**:** Immunochromatographic trial for determining antigens in a fast way, and without the use of equipment. In this study we refer to the TAR for SARS-CoV-2 diagnosis.

3 ETHICS

3.1 Revisions and Approvals of the trial's protocol:

- Revision and Approval: Quality Assurance, Instituto Finlay de Vacunas.
- Revision and Judgement: Investigations' Ethic Committee (CEI), of the International Health Center "La Pradera", Havana, Cuba.
- Revision and Approval: Centro para el Control Estatal de la Calidad de los Medicamentos, Equipos y Dispositivos Médicos (CECMED), Havana, Cuba.

Prior to the start of the study, the protocol was evaluated by the CEI of the International Health Center "La Pradera", in Havana, Cuba (ANNEX 5). In turn, the Health and Science CEI of Turin, Italy, approved an observational study on COVID-19 at the "Amedeo di Savoia" Hospital in that city, which supports the proposed study: *"STUDIO e-COVID. Study osservazionale sulla malattia COVID-19. Version 2.0 of 09.26.2021"*. These committees are formed in accordance with Good Clinical Practices (GCP), with the documents that support their constitution and the standard work procedures designed for their correct operation. Although formally, the evaluation of the CEI of the clinical site in Cuba, where recruitment, inclusion and vaccination will take place, is required, the CEI in Italy was also kept informed about the progress of the study. Both committees participated in the study, depending on the stage developed in Cuba or Italy.

The opinion issued by the CEI of "La Pradera", together with the documentation of the study, was delivered to the CECMED for review and approval. Once approval was obtained by the CECMED, the clinical study began. On the other hand, during the entire study, auditing visits took place by the Quality Assurance Division of the Instituto Finlay de Vacunas and the Centro Nacional Coordinador de Ensayos Clínicos, which watched over compliance with ethical standards.

Creation took place of a data-handling independent committee: CIMD (from Spanish Comité Independiente de Manejo de Datos) (ANNEX 5), according to GCP, which has the document supporting its constitution and the procedures designed for proper functioning. This committee had, among its missions, the analysis and report on safety, associated to each dose applied, to show evidences on the research product´s safety. Also assessed were the immunogenicity analyses.

In addition to keeping the regulatory authorities and MINSAP informed on the trial, there were agreements or contracts signed among the participating institutions before the study's start, and a

meeting took place with all the participants in the research for the protocol discussion and criteria unification.

3.2 Ethical aspects in the assays' conduction

As already mentioned, the clinical trial protocol followed the ethical principles for medical research with human beings, established in the updated Helsinki Declaration at the 64th General Assembly, Fortaleza, Brazil, October 2013.

►Justification of the study's determinations. Objective of the determinations:

- Microbiology laboratory: to determine whether the subject is infected by the SARS-CoV-2.
- Immunology laboratory: to assess the immunologic response enhanced by the vaccine.

►Ethical justification of the study's design:

The trial design was based on the evaluation of a dose of SOBERANA® Plus ST in convalescents from COVID-19 (not evaluated) and in individuals from Italy who had previously been vaccinated with another vaccine against SARS-CoV-2, with the Reactogenicity and immunogenicity data were obtained. This study made it possible to obtain information that increased knowledge about the immune response induced by SOBERANA® Plus ST in the population studied, and as a consequence, about the probability of success of future research. The design was based on the results of the Phase I, II clinical studies that have used SOBERANA® Plus ST in convalescents, as well as the use of this vaccine as a third dose in a heterologous scheme with the SOBERANA® vaccines during Phase I, II and III, which have endorsed its safety and immunogenicity.

► Proper preparation for facing possible adverse events and for assurance of the subjects' safety:

The study established an active and passive ambulatory vigilance during 28 days after the dose administration.

- At the clinical site, immediately after vaccination, vigilance for 1 hour took place. The clinical site had available a Cardiac Arrest Cart and Urgency Stock, and the adverse events received treatment according to the protocols for adult patients' handling and treatment.
- During the first 7 days post-vaccination, monitoring took place on solicited local and systemic adverse events, through face-to-face consultations during the first 72 hours. On the subsequent days: 4, 5, and 6, passive vigilance took place, and on day 7 there was a face-to-face consultation (Cuba).
- For 28 days, unsolicited adverse events were monitored through passive surveillance and on day 28 a final face-to-face consultation in Italy.

- Serious adverse events monitoring took place for 28 days, although there was none detected during the entire study.
- An electronic Adverse Events Diary was enabled for safety monitoring by the subject included in the study.

► Ethical responsibilities of all participants in the research:

a) Clinical researchers: To assure adherence to the protocol and compliance with the procedures it establishes. To provide information to the subjects, and to request their consent. To keep confidentiality on the information generated in the study.

b) Institution: To assure the facilities' maintenance and their proper utilization by the researcher.

c) Research team: To assure compliance with the protocol, and with the procedures established by the Promoter. To keep confidentiality on the information generated in the study.

d) Promoter: To assure compliance with GCP in the protocol design, to assure compliance with the GMP in manufacturing the vaccinal candidate to use in the study.

e) Monitor: To verify compliance with GCP, and to watch over the protocol's proper execution.

f) CEI: To review and to give their judgement on the trial's protocol and to verify the study's progress.

g) CIMD: To keep confidentiality on the information generated in the study.

h) CECMED: To safeguard the subjects' integrity through the trial's revision, approval, and monitoring.

► Issues about confidentiality:

All information on the trial is confidential. Established was that:

- ✓ The Researcher/Institution assures that revelation to third parties on information about the trial shall not occur, in any way, without the volunteers' consent in writing.
- ✓ The rights and welfare of the human subjects become protected. They will learn that both the results of the laboratory studies and the samples of the body fluids are duly protected and will be preserved only while they remain useful for the aims that justified their collection, and not for any other purpose, non-declared in the study protocol, unless the subject undergoing research had given explicit consent for other later use, in case it becomes necessary.
- ✓ The data informed in this trial will be exact, complete, and verifiable from the original sources.

- ✓ The study's results will be part of a final report, structured according to Annex 5 of the Regulation 21-2008 of the Cuban Regulatory Agency, CECMED. Said report is for delivery to CECMED and the study's CEI.
- ✓ The researcher will have the right to publish, or allow the publication, of any information or material related to the work, previous consideration by the Promoter, who might ask for its deferment, in case it becomes necessary to protect any intellectual property rights of the product or any other aspect.
- ✓ The promoters representing the protocol should receive beforehand any proposal for presentation (manuscript, summary, poster, or any other modality) for its sending to a scientific journal or event, along with the confirmation that the rest of the authors have reviewed it and that they agree with the said the proposal for publication or presentation.
- ✓ The Promoter commits himself to comment such documents in a period of 10 days.
- ✓ All rights and interests in any invention, expertise or other intellectual property rights generated during the development of the clinical study object of this protocol, shall constitute and remain in the promoter´s property.

Each subject of the study will keep updated about the individual results of the research, after the codes' opening and the database closure. The community's health authorities will keep updated on the global results of the investigation, in both cases through the clinical sites' researchers in charge.

3.3 Information to the subject and consent:

The information to the subjects was done in Italian, the different specialists participating in the study had access to the documentation in the relevant language: spanish or italian, depending on their nationality. The Clinical Investigators informed the subjects of the study design, the vaccine to be investigated, and their background. All this information was provided orally and in writing, in simple and accessible terms, with the aim of achieving understanding. Each subject was informed that in the rare event that he suffered any harm as a direct result of the study, he would be guaranteed full medical care, in Cuba or Italy.

Additionally, subjects received assurance that all information generated through the study would remain properly guarded, so to grant confidentiality on their personal data, as well as that they will learn about any other information that might become relevant during their permanence in the study; and as well that they would be free to abandon the study without prejudice. The subjects, after having received all the information regarding the trial, and after a prudential time to analyze the information received, decided freely on their participation in the study, and signed the “Informed Consent Form” (ANNEX 4), keeping a copy of this document for themselves.

4 GENERAL INFORMATION ON THE STUDY. RESEARCHERS AND ADMINISTRATIVE STRUCTURE

Title:

"Exploratory study of the SOBERANA® Plus ST vaccine, to evaluate its reactogenicity and immunogenicity in adults from Italy: convalescents from COVID-19, and in subjects with no history of this disease previously immunized against SARS-CoV-2".

Name of the medicament:

SOBERANA® Plus ST (Vaccine based on dimeric RBD of the virus SARS-CoV-2 in aluminum hydroxide gel).

Indication:

Prophylactic Vaccine against COVID-19.

Abbreviated Title:

SOBERANA PLUS TURIN.

Protocol identification code:

IFV/COR/16.

Cuban Public Clinical Trials Register:

00000397.

Investigation Phase:

Exploratory study.

Promoting Center:

Instituto Finlay de Vacunas (IFV).

Trial's Starting Date:

November 16, 2021.

Trial's Ending Date:

December 14, 2022.

Promoter's researcher:

Dr. Rolando Felipe Ochoa Azze. Medical Doctor, I and II Grade Specialist in Immunology. Dr. in Medical Sciences, Titular Researcher, Titular Professor and Consultant. Address: Calle 21 entre 198 y 200, Atabey, Playa, P.O. Box 16042. Havana, Cuba; C.P. 11600. Phone: 7271-8331.

Promoter's Representative:

Dr. Dagmar García Rivera. Dr. in Pharmaceutical Sciences, Titular Researcher. Address: Calle 21 entre 198 y 200, Atabey, Playa, P.O. Box 16042. Havana, Cuba; C.P. 11600. Phone: 7271-8331.

Monitors:

Centro Nacional Coordinador de Ensayos Clínicos (CENCEC).

Names and Surnames	Phones
MSc. Pedro Pablo Guerra Chaviano	72164207 / 72164220 / 72164221
Lic. Analeys R. Maceo Sinabele	
Lic. Anabel Amador González	
Lic. Leani Martínez García	

Promoter's Medical Expert:

Dr. Arturo Chang Monteagudo. Medical Doctor, I Grade Specialist in Comprehensive General Medicine and in Immunology. Master in Sciences in Biochemistry. Assistant Researcher, Assistant Professor. Instituto de Hematología e Inmunología. Address: 8 Street No. 460 between 17 and 19. Vedado, Plaza de la Revolución, C.P. 10400. Havana, Cuba. Phone: 7846-1146 / 7830-5553.

Main Researcher:

Dr. Vladimir Daniel Trujillo Machado. Medical Specialist of I Degree in Internal Medicine. International Health Center "La Pradera". Address: 15 Street No. 22210 between 222A and 234, Siboney, Playa, Havana, Cuba. Phones, 72725273; 72731441.

Researchers at the Participating Centers:

(See ANNEX 6)

General ethical considerations of the research:

This clinical trial protocol followed the ethical principles for conducting medical research in human subjects established in the Helsinki Declaration, updated at the 64th General Assembly, Fortaleza, Brazil, October 2013.

Prior to the start of the study, evaluation took place of the protocol by the Research Ethics Committee

(from Spanish: Comité de Ética de las Investigaciones (CEI), at the International Health Center “La Pradera”). This committee’s formation complies with the Good Clinical Practices (GCP); it holds the document backing its constitution, as well as the standard operational procedures designed for its correct functioning. The Committee was permanently aware of the study’s progress, and participated in its stages. The Cuban regulatory agency: Centro para el Control Estatal de la Calidad de los Medicamentos, Equipos y Dispositivos Médicos (CECMED) received the judgment granted by the CEI, along with the study’s documentation, for its revision and approval. Once received the CECMED approval, the clinical trial started. The CEI of Health and Science of Turin, Italy, of the "Amedeo di Savoia" Hospital of that city was consulted and kept informed, with emphasis on the phase of the study carried out in Italy.

Prior to the subjects’ inclusion in the study, they received information in Italian related to the trial, and to the vaccine, aimed at obtaining their consent to participate in it, duly signed and dated. The subjects received a duplicate of the Consent Form for them to keep it.

The Recruiting Process had into account an adequate evaluation rhythm, aiming at not exceeding the required number of subjects.

Creation took place of an independent committee for data monitoring, the Comité Independiente de Monitoreo de Datos (Spanish: CIMD), formed according to the GCP, which holds the document backing its constitution, and the procedures designed for its proper functioning. This committee had, among its missions, the responsibility to make the analysis and report on safety, associated with the dose applied, thus making it possible to show evidences on the research product’s safety. They also assessed the analysis on immunogenicity.

The staff in charge of the trial duly guarded all the individual information related to the subjects during the study, thus assuring confidentiality. The files containing all documentation generated during the study remains in “La Pradera”.

Start date of the preparation of the Final Report: February 10, 2022

Completion Date of the Final Report: July 4, 2022

General schedule:

N	Stage/ Activity	Starting Date
1	Planning/Protocol preparation	Agust-October 2021
2	Planning/Execution preparation	Agust-October 2021
3	Protocol delivery to the CEI	October 15, 2021
4	CEI Judgment	October 19, 2021
5	Protocol delivery to CECMED	October 19, 2021
6	CECMED Authorization for the Clinical Trial to start	November 12, 2021
7	Clinical Trial Start Workshop	November 12, 2021
8	Pre-recruitment process, evaluation	October 18 – November 10
9	Subjects recruitment's / informed consent	November 16, 2021
10	Inclusion and Vaccination start	November 16, 2021
11	Samples' processing / Data base feeding / Processing and statistical analysis / Final report preparation	November 16, 2021–march 31

5 INTRODUCTION

COVID-19 is characterized by a higher lethality in individuals with quantitative or qualitative impairments of immunity and with the presence of comorbidities (1-7). Regarding the possibility of suffering from the disease again, there are different criteria: some researchers report immunity depending on the levels of neutralizing antibodies. Other studies provide evidence of reinfection, especially in the face of the emergence of new variants of SARS-CoV-2 (4,8-11).

Neutralizing antibodies against SARS-CoV-2 are stimulated by the S1 subunit of the spike protein, especially the ACE2 receptor binding domain (RBD). For this reason, RBD-based vaccine candidates have been developed that have demonstrated their safety and immunogenicity, including the SOBERANA® series (10,12-14).

There are different criteria regarding the need to use booster doses. Some researchers have proposed them taking into account the progressive decline in protection induced by vaccines. Others point out that they are justified only to individuals with a poor response (15-19). Some specialists consider that boosters are questionable, since their use could reduce the availability of vaccines in developing countries, thus increasing inequities (15,20-22). However, booster doses with homologous and heterologous schedules have already been introduced in several countries (17,19,22,23), and high immunogenicity is reported, although safety concerns remain (19,22,23).

We must bear in mind that SOBERANA® Plus, a subunit vaccine, has been shown to be very safe and immunogenic, both in naïve and convalescent individuals, as well as an effective booster in people previously immunized with other SOBERANA® series vaccines. Therefore, we consider that it could behave in the same way with vaccines based on other platforms.

To continue the clinical evaluation of SOBERANA® Plus ST, an exploratory study was proposed to evaluate the reactogenicity and immunogenicity of a dose of said vaccine in adults from Italy, convalescing from COVID-19, and individuals with no history of having suffered from this disease. disease and previously immunized against SARS-CoV-2. All between 19 and 59 years of age and who give their consent to participate.

The evaluation of immunogenicity was carried out through the determination in Cuba of the levels of specific anti-RBD antibodies and the in-vitro inhibition of the ACE2:RBD interaction, as well as viral neutralization against different variants of SARS-CoV-2. at the “Amedeo di Savoia” Hospital in Turin, Italy and at the Cuban Civil Defense Laboratory.

6 OBJECTIVES AND HYPOTHESIS

6.1 General Objective:

To asses reactogenicity and immunogenicity of the SOBERANA® Plus ST vaccine against SARS-CoV-2 in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS -CoV-2.

6.2 Specific objectives:

1. To evaluate the reactogenicity of a dose of SOBERANA Plus ST in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS-CoV-2.

2. To evaluate the immunogenicity of a dose of SOBERANA Plus ST in adults from Italy: convalescents from mild or moderate COVID-19, as well as in subjects with no history of having suffered from this disease and previously immunized against SARS-CoV-2.

6.3 Working hypothesis

We did not propose working hypotheses for this exploratory study. We believe that their results would serve as a basis for building hypotheses for future studies.

7 RESEARCH PLAN

7.1 Trial's general design

Exploratory study of the SOBERANA Plus ST vaccine, prospective, open, uncontrolled, in parallel groups and multicenter (Cuba and Italy), to evaluate the reactogenicity and immunogenicity of a dose of this vaccine in adults from Italy (Fig. 1).

Population: It was planned to include two groups:

1) Up to 30 convalescents from Italy with a history of mild or moderate clinical symptoms of COVID-19. Adults, of any sex, between the ages of 19-59, who gave their consent to participate and who met the selection criteria.

2) Up to 30 volunteers from Italy, healthy, of either sex, between the ages of 19-59, with no history of having suffered from COVID-19 and vaccinated against SARS-CoV-2, who gave their consent of participation and that they met the selection criteria.

The convalescent group was not evaluated. Only three arrived in Havana, as we will explain in the corresponding section, and all were excluded from the study.

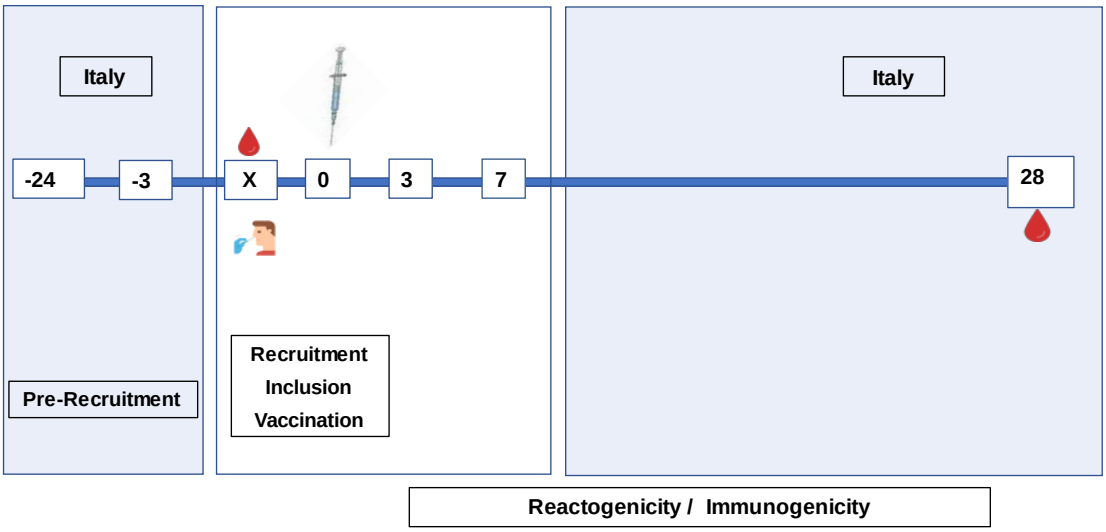

Fig. 1 Study design.

Legend: Blood sample for immunological studies TRA: Spanish: Test Rápido de Antígenos (Rapid Antigens Test).

Documentation:

Protocol: Delivered to the Regulatory authority. Version 1,0

Modifications to the Protocol: Not requested

Data Collection Notebook (Spanish: CRD): Annex 3

CIMD: See Annex 5

Practical Considerations:

We summarize them in the following Table:

Table 1. Distribution of activities.

Days:	Italy	Cuba: Vaccination and Surveillance adverse events						Italy	
	-24 to -3	Arrival	0	1	2	3	7	--	-- to 27	28
Pre-Recruitment	X									
Selection criteria	X		X							
TRA/PCR sampling		X								
Rapid pregnancy test			X							
Recruitment			X							
Inclusion			X							
Immunological laboratory			X							X
Vaccination			**X**							
Face-to face consultation		X	X	X	X	X	X			X
Non-face-to face consultation								X	X	
CRD completion			X	X	X	X	X	X	X	X
Adverse event diary			X	X	X	X	X	X	X	X
HC			X	X	X	X	X	X	X	X

Notes:

Days -24 to -3: Period of time in which the pre-recruitment of volunteers in Italy takes place.

Day of Arrival: PCR or TRA is performed upon arrival in Cuba.

Day 0: Inclusion and Vaccination.

Days 1,2,3,7: Face-to-face consultations in Cuba, active surveillance of adverse events.

Return to Italy and until day 28: The Italian investigators must continue to evaluate the occurrence of adverse events during the rest of the study, passively through the Adverse Events Diary and with a

Face-to-Face Consultation on day 28. Perform immunological determinations; completion of documents; reports to the Promoter in Cuba and results of the study to the volunteers.

CRD: Data Collection Notebook (Electronic).

Diary E.A: Diary of Adverse Events.

HC: Clinical History.

PCR or TRA for SARS-CoV-2: (Cuba).

Pregnancy test: (Cuba) will be carried out when appropriate.

Immunology: (The studies will be carried out before vaccination and 28 days after vaccination)

a) Determination of anti-RBD IgG antibodies. (Cuba).
b) Determination of in-vitro inhibitory antibodies of the RBD:ACE2 union and the inhibitory titer 50 (Cuba).
c) Neutralization test with different strains of active viruses (at the “Amedeo di Savoia” Hospital, Turin, Italy, and at the Civil Defense Laboratories in Cuba).

CENCEC monitors, and CENCEC auditors (ANNEX 9), as well as those of the IFV Quality Assurance Division, executed the monitorization and audit plan to the clinical trial.

7.2 Discussion on the trial design

The trial design was based on the evaluation of a dose of SOBERANA® Plus ST in convalescent patients with COVID-19 from Italy and in individuals who had previously been vaccinated with another SARS-CoV-2 vaccine, with whom we expected to obtain data of reactogenicity and immunogenicity that will increase the knowledge about the immune response induced by this vaccine in the studied population, and as a consequence, about the probability of success of the next investigations. The design was based on the results of the Phase I and II clinical studies that have used SOBERANA® Plus ST in convalescent patients, as well as the use of this vaccine as a third dose in a heterologous scheme with the SOBERANA® vaccines during Phase I, II and III, which have endorsed its safety and immunogenicity.

7.3 Selection of the subjects

A pre-recruitment was carried out in Italy by the Italian Researchers, a process controlled electronically by the Principal Investigator and the Promoter in Cuba. After arrival in Cuba, the final selection of the subjects was carried out by the Clinical Investigators designated for this purpose, led by the Principal Investigator of the study.

7.3.1 Universe of the study and diagnosis criteria

Male and female subjects aged between 19 and 80 years, of Italian nationality, with permanent residence in Italy, with antecedents of COVID-19, with mild or moderate clinical picture after 2 months of being discharged with a negative PCR or TRA; and apparently healthy individuals, with no history of COVID-19 and previously immunized with other SARS-CoV-2 vaccines between 3 and 12 months before the start of the study.

Following, the criteria for selection considered:

7.3.2 Inclusion criteria (both groups):

1. Subjects granting their informed consent in writing for participating in the study.
2. Subjects aged between 19 and 59 years.
3. Body mass index between 18,5 and 34,9 kg/m^2.

7.3.3 Exclusion criteria:

A) Convalescents from COVID-19:

1. Subjects with COVID-19 antecedents, complying with any of the following criteria:
   a) Current history of infection, or of having received medical discharge by SARS-CoV 2 during 2 months before recruitment.
   b) Antecedents of serious, or critical COVID-19 clinical picture. Likewise, asymptomatic (subclinical) COVID-19 cases would be excluded from the study.
2. Subjects with febrile or acute infectious disease in the 7 days prior to administration of the vaccine or at the time of administration.
3. Subjects with antimicrobial treatment or sustained treatment with NSAIDs in the 7 days prior to the administration of the vaccine.
4. Subjects with chronic NON-communicable NON-controlled diseases, according to clinical or laboratory criteria (eg: bronchial asthma, chronic obstructive pulmonary disease, ischemic heart disease, arterial hypertension, diabetes mellitus, thyroid, neurological, hemolymphopoietic system diseases, chronic hepatitis, liver failure, kidney failure, psychiatric illness at the psychotic level, among others).
5. Subjects with congenital immunodeficiencies, or unresolved acquired immunodeficiencies.
6. Subjects with a history of neoplastic disease that is not in complete remission.

7. Subjects with a history of substance abuse during the last 30 days or addictive disease to toxic substances, except smoking.
8. Subjects with diminished mental faculties.
9. Subjects with a history of severe allergic disease (anaphylactic shock, angioneurotic edema, glottic edema, severe urticaria).
10. Subjects with a history of hypersensitivity to any of the components of the vaccine.
11. Participation in a clinical trial of preventive or therapeutic intervention in the last 3 months.
12. Application of any other vaccine against COVID-19.
13. Application of another preventive or therapeutic vaccine in the last 30 days.
14. Treatment with immunomodulators (either immunopotentiators or immunosuppressants) in the last 30 days. Examples: steroids (except occasional use of topical or inhaled steroids), cytostatics, interferon, immunoferon, transfer factor, monoclonal antibodies, any gamma globulin, levamisole, thymosin, etc. In the same way, those people who, due to their underlying disease, require immunomodulatory treatment and who may coincide during the development of the study should be excluded.
15. History of having received a blood transfusion or blood products in the last 3 months.
16. Subjects with difficulties in attending scheduled follow-up consultations.
17. Splenectomy or splenic dysfunction.
18. Women of childbearing potential DO NOT use reliable contraceptive methods during the study.
19. Pregnancy, puerperium or lactation.
20. Subjects with tattoos in the deltoid region of both arms.Sujetos con enfermedad febril o infecciosa aguda en los 7 días previos a la administración de la vacuna o en el momento de su aplicación.

B) Subjects previously immunized against SARS-CoV-2

1. Subjects with a history of having suffered from COVID-19 in any of its forms.
2. Subjects with febrile or acute infectious disease in the 7 days prior to administration of the vaccine or at the time of administration.
3. Subjects with antimicrobial treatment or sustained treatment with NSAIDs in the 7 days prior to the administration of the vaccine.
4. Subjects with chronic NON-communicable NON-controlled diseases, according to clinical or laboratory criteria (eg: bronchial asthma, chronic obstructive pulmonary disease, ischemic

heart disease, arterial hypertension, diabetes mellitus, thyroid, neurological, hemolymphopoietic system diseases, chronic hepatitis, liver failure, kidney failure, psychiatric illness at the psychotic level, among others).

5. Subjects with congenital immunodeficiencies, or unresolved acquired immunodeficiencies.
6. Subjects with a history of neoplastic disease that is not in complete remission.
7. Subjects with a history of substance abuse during the last 30 days or addictive disease to toxic substances, except smoking.
8. Subjects with diminished mental faculties.
9. Subjects with a history of severe allergic disease (anaphylactic shock, angioneurotic edema, glottic edema, severe urticaria).
10. Subjects with a history of hypersensitivity to any of the components of the vaccine.
11. Participation in a clinical trial of preventive or therapeutic intervention in the last 3 months.
12. Application of a vaccine against SARS-CoV-2 that is not included within the interval between 3 and 12 months before recruitment.
13. Application of another preventive or therapeutic vaccine in the last 30 days.
14. Treatment with immunomodulators (either immunopotentiators or immunosuppressants) in the last 30 days. Examples: steroids (except occasional use of topical or inhaled steroids), cytostatics, interferon, immunoferon, transfer factor, monoclonal antibodies, any gamma globulin, levamisole, thymosin, etc. In the same way, those people who, due to their underlying disease, require immunomodulatory treatment and who may coincide during the development of the study should be excluded.
15. History of having received a blood transfusion or blood products in the last 3 months.
16. Subjects with difficulties in attending scheduled follow-up consultations.
17. Splenectomy or splenic dysfunction.
18. Women of childbearing potential DO NOT use reliable contraceptive methods during the study.
19. Pregnancy, puerperium or lactation.
20. Subjects with tattoos in the deltoid region of both arms.Sujetos con antecedentes de haber padecido COVID-19 en cualquiera de sus formas.

7.3.4 Exit criteria:

Exit criteria not defined.

7.3.5 Interruption criteria:

1-Voluntary Abandonment.

2-Emergence of serious adverse event with causality relationship.

3-Subject who, at any time of the study, becomes PCR positive to SARS-CoV-2, by Rapid Antigen Test or PCR test.

4-Decision of the clinical researcher, based on changes in the patient´s clinical condition, justifying interrupting the patient's participation in the clinical trial.

5-Subject's death.

7.4 Treatment:

7.4.1 Administered treatment

Only one treatment group was included:
Experimental Group: 50 µg d-RBD+ Aluminum Hydroxide Gel, IM route in the deltoid region, volume 0,5 mL, one dose.

7.4.2 Product's Identification

SOBERANA Plus ST vaccine is an injectable suspension; presented in a 2R vial, one-dose, for single use, containing a volume of 0,7 mL; for 0,5 mL vaccination.

La vacuna es una suspensión inyectable; se presentó en bulbo 2R, unidosis, para uso simple, con retapa de color carmelita; contiene un volumen de 0,7 mL; a vacunar 0,5 mL. Each bulb was identified with the labels of the finished product, taking into account that it is an open study.

Every dose (0,5 mL) of SOBERANA® Plus ST **Lote 1006SP** contains:

Table 2. SOBERANA® Plus ST composition.

Components	Quantity per dose (0,5 mL)
Active substances	
Dimer of the ACE2 receptor binding domain (RBD) of the S1 protein	50 µg
Excipients	
Thiomersal	0,05 mg
Disodium Phosphate Hydrogen	0,03 mg
Sodium Phosphate Dihydrogen	0,02 mg
Sodium Chloride	4,25 mg
Water for Injection, cs	0,5 mL
Adjuvant	

Packing consisted in cases with capacity for 20 vials each. Identification of the packing cases consisted in a label identifying the parcel as a product for clinical trials.

Preservation of the Research Product: The vaccines' preservation temperature is 2 to 8 °C. You should not use them if they had been exposed to freezing temperatures; thus, the person in charge of the Research Product Handling performed daily controls (three times a day) of the temperature in the fridges for the Research Product's storage. During the Research Product's stay at the vaccination site, the vaccines kept refrigerated in thermal boxes, equipped with devices for temperature measurement, which took place every 30 minutes by the Nurse who prepared and applied the vaccinal candidate. The temperature controls assured the cold chain preservation, following the regulations established by the Sistema Nacional de Salud (National Health Service) and the Instituto Finlay de Vacunas (IFV). The person in charge of handling the Research Product in the IFV was responsible for transferring the vaccines up to the clinical site, complying with the quantity of vaccinal candidate to use and the regulations established for the Research Product´s transfer activity.

Measures for assuring safety during the product's handling: A trained nurse, certified for this vaccination procedure, was the one to apply the vaccinal candidate. Administration took place of 0,5 mL of the research product, by IM route in the deltoids. The syringes and needles used were disposable ones. The syringes to use should have 0,5 mL capacity, and the needles to use were 23G x 1". The proper administration techniques were the ones corresponding to the procedures for applying vaccines by IM route. Verification took place on the suspension's uniformity before administering the vaccine. A CIMD representative could verify the product's administration process.

Conduct to follow with the Research Product's used vials: Once the vaccination concluded, the process with the used vials was to put them into their packaging case, sealed with a label stating "Used Product," and to transfer them to the "La Pradera" for 7 days, at temperature between 2 -8 ºC, where the Promoter collected them. The Promoter proceeded with the vials' destruction at the end of the study.

7.4.3 Assignment-to-treatment methods

The study is not randomized. The vaccine in the proposed strength will be administered to the subjects of both groups included in the study.

7.4.4 Dose selection

In the clinical studies using RBD as the vaccinal immunogen, the potencies assessed were between 5 and 50 µg/dose; therefore, our formulation falls within the range evaluated in other different vaccinal candidates, similar to ours.

The decision to use one dose only took place by considering that the volunteers participating in the study have already been in contact with the SARS-CoV-2; thus, they should have memory B cells; therefore, one dose of the vaccine should act as a booster, increasing the protective antibody levels.

In our preclinical studies, assessment of the potency proposed for the clinical trial took place with experimental batches and GMP batches, which demonstrated satisfactory results, both in terms of safety and immunogenicity. It should be worth considering, that the RBD employed is the same one usually employed in clinical assays in our country, registered under the code: RPCEC00000332 (SOBERANA 01), RPCEC00000338 (SOBERANA 01A), RPCEC00000340 (SOBERANA 02), RPCEC00000347 (SOBERANA 02A), RPCEC 00000349 (SOBERANA 01B), RPCEC 00000366 (SOBERANA Plus), RPCEC00000354 (SOBERANA 02-Fase III), in which the safety of the vaccine immunogen has been demonstrated.

7.4.5 Blinding

The studio is open. Each bulb will be identified with the finished product labels.

7.4.6 Concomitant treatment

The administration of immunomodulatory drugs was an exclusion criterion from the study. The medications that the subject consumed before starting the study were recorded, as well as the reason for the indication, daily dose, start date, and how long it had been used. Likewise, all those medications that the subject consumed during the study were recorded in the Clinical History and the CRD (ANNEX 3).

7.4.7 Treatment compliance

Once the subjects had been vaccinated, the vaccinating nurse completed the Investigational Product Administration Record, with the date and time of vaccination and the subject's signature as proof that they received the vaccine or placebo; In addition, the dose and volume applied, as well as the anatomical area of application of the product, were reflected in the Clinical History.

No serious adverse events related to vaccination were detected during the study, so it was not necessary to stop the trial. Similarly, the study was not interrupted in any of the participating subjects.

7.5 Efficacy and safety variables:

7.5.1 Efficacy and safety measurements

Vigilance on safety and reactogenicity remained active during this Phase II trial. We define Adverse Event (AE) as any unfavorable medical event occurring in a clinical research's patient or subject, who received a pharmaceutical product, which does not have necessarily a causal relationship with this treatment.

A Serious Adverse Event (SAE) is any unfavorable medical occurrence ending with death, life threatening, resulting in persistent or significative disability/incapacity, requiring the subject's hospitalization or prolongation of the current hospitalization, or causing congenital abnormality in the subject´s descendance. Moreover, one should consider as serious, those important adverse events that might endanger the subject, or require interventions for preventing any of the above-mentioned results.

On the other hand, an Adverse Reaction (AR) occurs when between a product and an adverse event, a rational possibility exists of causal relationship, or when one cannot rule out a relation between them.

An Unexpected Adverse Event (UAE) is one which nature or seriousness is inconsistent with the information available on the product.

► Solicited Adverse Events

The Requested Adverse Events included a group of local and systemic adverse events that have been reported more frequently in vaccines with a similar composition to the one under investigation, especially taking into account those detected in other clinical trials in which SOBERANA® Plus ST was used. These events were actively monitored during the first 7 days after vaccination. They were recorded by the subject in the Adverse Events Diary, and subsequently described in the clinical history by the physician.

These events were recorded in the CRD in the models corresponding to Local Solicited Adverse Events and Systemic Solicited Adverse Events, during the first 7 days of vaccination.

► Local solicited adverse events (injection site):

Records of the following local adverse events appear in the Adverse Events Diary during the first 7 days (**Table 3**):

Table 1. Local Solicited Adverse Events, definition, and intensity.

Adverse event	Definition	Intensity		
		Mild	Moderate	Severe
Pain at the injection site	Unpleasant feeliing associated with a potential damage of the tissue, occurring at the injection site.	Pain when touched	Pain when moving the limb	Spontaneous pain, preventing the execution of daily activities
Erythema	Reddening surrounding the injection zone, which disappears at vitro pressure, and reappears when it ends.	>0 a <2.5 cm	≥2.5 and <5 cm	≥5 cm
Increase in Volume	Increase in volume at the injection site, typically caused by infiltration of liquid into the tissue. It might cover the complete limb in severe cases. Generally, it is soft to touch, although, in some cases it can be firm, in dependence of the space available for the liquid to accumulate. It differs from induration in that the latter is firmer to touch, and with sharper borders. The edema can appear accompanied by erythema and sensitivity (classic features in an inflammatory reaction).	>0 a <2.5 cm	≥2.5 and <5 cm	≥5 cm
Induration	Pathological tissue induration at the injection site, firm to palpation, with sharp borders; it includes dermis, epidermis, subcutaneous and adipose tissue, and muscle, it can exist independently or concomitantly with other local reactions. For describing it one needs to touch it and feel it, not just to observe it; its form is flat, unlike the nodule, which is round.	>0 a <2.5 cm	≥2.5 and <5 cm	≥5 cm
Local heat	Heat at the vaccination site.	Local heat surrounding the injection zone, mild enough as for the subject not requiring medication.	Local heat covering the entire deltoid region, which requires local anti-thermal measures	Local heat covering the entire arm's region, accompanied by other phlogistic signs, requiring medication.

For identifying local adverse events, the following algorithm was of use.

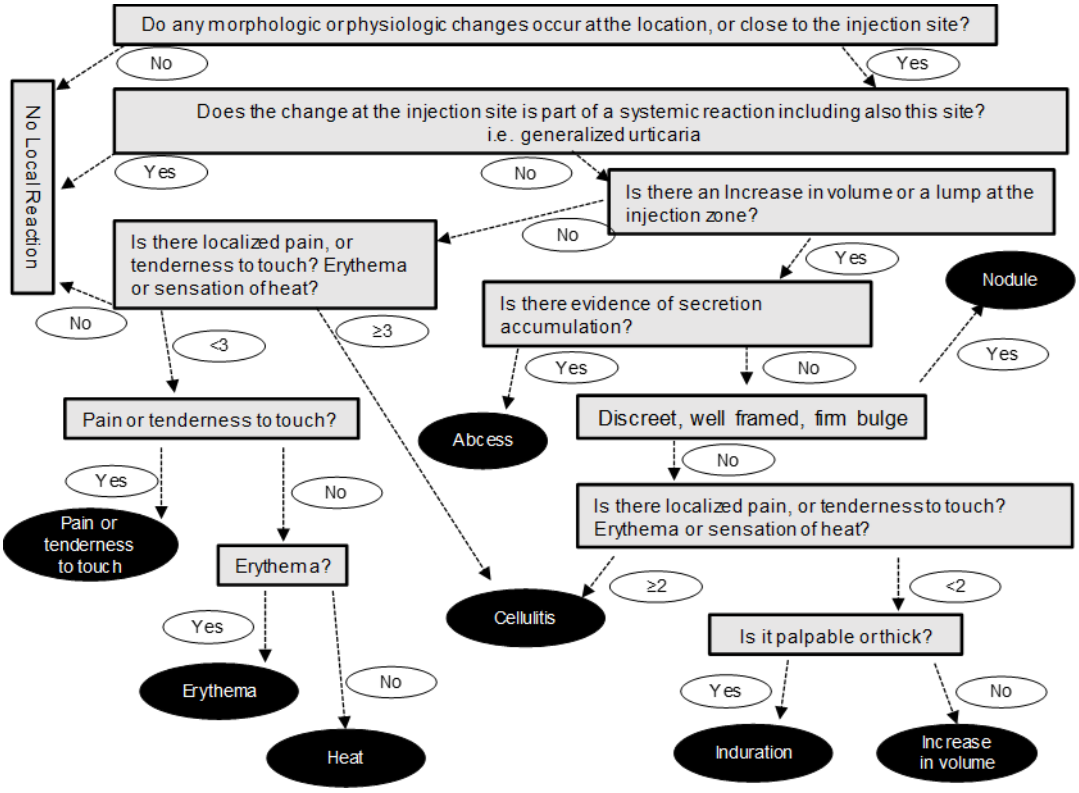

Fig. 2. Algorithm for identifying local Adverse Events

►Systemic Adverse Events:

The following systemic adverse events appeared in the daily card during the first 7 days:

Tabla 2. Solicited systemic adverse events, definition and intensity.

Adverse Event	Definition	Intensity		
		Mild	Moderate	Severe
Fever *	Increase of endogenous origin in the body temperature, observed in at least one single measurement, equal to or greater than 38 ºC, Axillary temperature to measure.	≥38.0ºC to ≤39.0ºC	>39.0ºC to 40.0ºC	>40ºC
General discomfort	Disorder featured by a feeling of inconvenience, or general discomfort, a bad humor mood.	Restlessness or lack of well-being, well tolerated by the subject.	Restlessness or lack of well-being, interfering with the execution of daily activities	Restlessness or lack of well-being, preventing the execution of daily activities
Rash	Cutaneous rash featured by the presence of delimited blemishes, papules, or both.	Presence of blemishes or papules covering less than 10% of the body surface	Presence of blemishes or papules covering between 10 and 30% of the body surface	Presence of blemishes or papules covering more than 30% of the body surface

* ***Explanatory Note:*** *Temperature between 37 and 37.9 ºC (slight fever) appears in the Clinical Record, but, as it is not an Adverse Event, it has no record in the Data Collection Notebook (CDR).*

► Evaluation of non- solicited Adverse Events:

Collection took place of all adverse events occurred, up to 28 days after vaccination. The subjects or their relatives made records of them in the Adverse Events Diary, and were subsequently described and evaluated by the medical doctor in the clinical record and the CRD.

Assessment took place on the intensity of every non- solicited adverse event, according to the following criteria:

Grade 1: Mild: Adverse event that the subject can easily tolerate, causing minimum trouble, and not interfering with normal daily activities.

Grade 2: Moderate: Adverse event unpleasant enough as to interfere with normal daily activities.

Grade 3: Severe: Adverse event preventing the daily activities' execution.

The case definition used was the Brighton Collaboration, and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (24,25).

7.5.2 Measurements suitability

► Periodicity and method for measurement the Adverse Events:

- Post-vaccination adverse events were followed from the day of vaccination (Day 0) to 28 days later.
- On the day of vaccination (Day 0), the subjects were subjected to strict medical surveillance at the vaccination center by the team of selected researchers for 1 hour after administration of the vaccine.
- Once completed, the Clinical Investigator activated the subject's Adverse Event Diary (electronic) to be completed during the time he was not under medical observation. The same was presented by the subject in all the face-to-face evaluations planned in the study. The information collected in it, as well as the results of all the observations, were collected in the Clinical Records. The data to be completed in the CRD was made once the evaluation of the adverse event was concluded and closed.
- During the first 7 days post-vaccination, solicited local and systemic adverse events were monitored during the first 72 hours. On days 4, 5, and 6 following, passive surveillance was performed (non-face-to-face consultation) and on the 7th day, face-to-face consultation.
- For 28 days, unsolicited adverse events were monitored, adding a final face-to-face consultation on day 28.Se realizó seguimiento de los eventos adversos posteriores a la vacunación desde el día de la vacunación (Día 0) hasta 28 días después.

The information generated in these consultations was collected in the Clinical Records enabled for the study and then recorded in the CRD in their corresponding sections.

The Principal Investigator secured all necessary resources to treat any AEs that might occur during post-vaccination surveillance, including SAEs.

AEs were recorded in diagnostic terms, when this was not possible they were expressed as signs or symptoms.

The following data was collected for each adverse event:

- • Medical diagnosis or signs or symptoms
- • Start date and time
- • Treatment received
- • intensity
- • Gravity
- • Outcome
- • End date and time
- • Causal relationship with the vaccine

For the diagnosis of AE, the Brighton Collaboration case definitions and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (24,25) were used.

► Evaluation on the AE causality:

For causality evaluation, gathering took place of all necessary information (questioning, concomitant diseases, physical exam, clinical/microbiological laboratory results, Rx, drugs use, starting date and hour, duration, personal and family antecedents, etc.) to arrive at an accurate diagnosis, whenever possible.

The AEs' causality analysis took place by considering all elements required for its evaluation, and analyzed by a commission including the Main Researcher, the medical doctor who has been following the case, the epidemiologist, co-researchers, and the Promoter, using the WHO 2013 algorithm.

Causality relationship's report followed the terms below:

A: Causal association consistent with the vaccination.

B. Undetermined

C. Causal association inconsistent with the vaccination.

D. Not Classifiable.

► Evaluation during treatment (up to 28 days after vaccination):

All the information related to the initial evaluation and follow up of the subjects, appears in the Clinical Record and the CRD.

The programmed consultations took place by designed medical doctors, who had received adequate training. Through questioning, physical exam and revision of the Adverse Events Diary in every interview, collection took place of the data relative to the Adverse Events' emergence and monitoring. Also registered was the use of concomitant treatments, and the verification of the trial's inclusion/exclusion criteria, as well as those for the trial's interruption.

Table 3. Distribution of the laboratory determinations by evaluation time.

Determinations	Italy and Cuba Day 0	Cuba Day 0	Italy and Cuba Day 28	Cuba Day 28
TRA/PCR SARS-CoV-2	-	X	-	-
Pregnancy test	-	X	-	-
Anti-RBD Antibody	-	X	-	X
RBD / ACE2 Inhibition%	-	X	-	X
Inhibitory Titer 50	-	X	-	X
SARS-CoV-2 Neutralizing Antibody Titers	X	-	X	-

7.5.3 Main variables and criterion for evaluating efficacy and safety

A. Evaluation on reactogenicity

- **Independent Variables:** Age, Skin color, Sex, Treatment assigned, Time elapsed since medical discharge in the convalescent group, Time elapsed since vaccination against COVID-19 in the previously immunized group.
- **Dependent Variables:** Every Adverse Event that might emerge in the study. Definition for each event's emerged: time of emergence, duration, Intensity, seriousness, and outcome **(Table 6).**

Table 4. Description of the variables related to safety.

Variable	Type	Criteria	Evaluation
Description of the Solicited AE	Nominal	Any sign or symptom emerging after vaccination and up to 7 days after declared as a Solicited AE.	Percentage number
Description of the Non- solicited AE	Nominal	Any sign or symptom emerging after vaccination and before 28 days, which Is not among the solicited AEs.	Percentage number
AE Duration	Ordinal	• ≤24 hours • >24 - ≤48 hours • >48 - ≤72 hours • More than 72 hours	Percentage number
AE Emergence	Ordinal	• ≤60 minutes • >60 minutes ≤24 hours • >24 - ≤48 hours • >48 - ≤72 hours • More than 72 hours	Percentage number
AE Intensity	Ordinal	• Grade 1 or Mild • Grade 2 or Moderate • Grade 3 or Severe	Percentage number
AE Seriousness	Nominal	• Serious • Non-serious	Percentage number
AE Outcome	Nominal	• Recovered • Recovered with sequels • Persisting • Death • Unknown	Percentage number
Causality relationship	Nominal	• Causal association consistent with vaccination • Undetermined • Causal association inconsistent with vaccination. • Not classifiable	Percentage number

B. Evaluation on immunogenicity

- **Independent Variables:** Age, Race, Sex, Group, Assigned treatment, Time elapsed since medical discharge in the convalescent group, Time elapsed since vaccination against COVID-19 in the previously immunized group

- **Dependent Variables**

Table 5. Description of the variables related to immunogenicity.

Variable	Type	Criteria	Evaluation
Anti-RBD specific IgG antibody levels	Quantitative Continuous	IgG antibody levels.	Mean geometric titers (GMT) of the anti- RBD antibody levels and IC 95%. Correlation between the Anti-RBD IgG antibody levels with respect to the RBD: ACE2 inhibition % and to the neutralizing antibody titers.
		Seroconversion calculation will take place, defined as a 4-times increase of the Anti-RBD IgG antibody titers, with respect to the basal levels	Percentage number, IC 95%.
Neutralizing antibody titers	Quantitative Continuous	Neutralizing antibody titers, determined by neutralization test.	GMT of the neutralizing antibody titers and CI 95%. Correlation with respect to the anti-RBD IgG antibody levels and the RBD: ACE2 inhibition%
Inhibition% of the RBD: ACE2 interaction	Quantitative Continuous	Inhibition % of the RBD: ACE2 interaction within a dilution range starting 1/100. Determination of the ratio of subjects with inhibition ≥ 70% of the RBD binding to ACE2 at 1/100 dilution. Determination of TI50 and those with values ≥ 250 (value corresponding to 3 times the GMT value of the TI50 from the Cuban convalescent panel serum).	Median (IC 95%) Correlation with respect to: - Anti-RBD IgG antibody levels -Neutralizing antibody titers Number, percentage, IC 95%

* SARS-CoV-2 variants finally studied: D614G, beta, delta, omicron

7.6 Quality Assurance:

►Activities executed prior to the trial' start:

✓ A meeting took place with the Management of the Entities involved in the study, to report on the study's strategy and on the requirements regarding material and human resources assurance.

- ✓ Selection carried out of the research teams for every clinical site, analysis proceeded of each participant's Curriculum Vitae to define his/her functions within the investigation. Workshops for training executed, given by a team of selected researchers.

► Monitoring and Audits Program to the Trial's sites:

The CENCEC monitors and auditors (ANNEX 9), and those from the IFV Quality Assurance Division executed the Monitoring and Audits Plan in the Trial's sites.

Execution of all the quality control visits took place as per the monitoring plan, according to the critical points identified.

During these visits, verification took place of the research's proper execution, through the analysis of the compliance with the Protocol, the GMP and each site's standard operation procedures, the results of the informed consent process, as well as the completion of the registers included in the researcher's folder. Moreover, the proper CRD fill-up was object of verification, and its correspondence with the primary information contained in the Clinical Records; revision took place of the informed consents, among other aspects related to the research. Inventory of the product took place, with all the documentation reviewed, regarding the vaccination sites and sampling rooms.

The corresponding authorities received permanent information about the trial. Agreements or contracts were signed with the participating institutions, before of the study's start.

A meeting took place with all participants of the research for the discussion on the protocol and the unification of the criteria; and as well the Starting Workshop and the initial visits to all the institutions involved.

► Assurance of the indispensable resources:

The IFV complied with the vaccinal candidate's supply, as previously agreed. The rest of the necessary resources for the trial (disposable sterile syringes, disposable gloves, and other inputs required for conducting the trial) came from the IFV and MINSAP. Equally, the office supply for assuring the good development of the study became granted. The human resources required for the study were arranged by the Units of the Health System involved (ANNEX 6), after having coordinated it with the institutions' management. The Promoter, and the main researchers duly trained the researchers.

7.7 Statistical Methods

7.7.1 Statistical Analysis Plan

There were no modifications introduced to the analysis plan foreseen.

There were three populations identified a priori:

- Per protocol" (PP): defined as formed by those included individuals complying with all inclusion criteria, and with no exclusion criteria, who had received the planned dose, have available the data regarding the variables' valuation, and had not suffered any major protocol deviation.

  The following were considered as major deviations:

  - ✓ Use of concomitant therapy not established.
  - ✓ Failure to obtain informed consent, eg, no documentation, consent obtained after initiation of study procedures.
- "By Intention to treat" (ITT): All included and vaccinated individuals would be considered, regardless:

  - ✓ their adherence or not to the criteria for entry,
  - ✓ abandonment of the study,
  - ✓ protocol deviations

  In this population the aspects planned for their study were variables on safety, and within the effect variables, the immunologic evaluations: specific antibodies, inhibition %, RBD: ACE2 and neutralizing antibodies.
- "Safety population": will include all vaccinated individuals.

Verification took place of the compliance with the inclusion and exclusion criteria.

Following appears the summary of all variables involved (control, independent, main, and secondary variables):

- for quantitative variables, the central trend and dispersion measurements: number of observations available, mean, median, standard deviation, minimum, maximum, interquartile range, 25 and 75 percentiles.
- for qualitative variables, the frequency distributions.

In each study subgroup (convalescents / healthy vaccinated).

►Adverse Events. Reactogenicity profile:

- ✓ The frequency of individuals with serious adverse events related to the administration of the vaccine was estimated and the corresponding 95% confidence interval will be calculated. In

case the frequency is very low or very high, the confidence interval will be estimated using the Bayesian approach.

- ✓ The frequency of individuals with each adverse event was estimated.
- ✓ The frequency distributions of each type of reported event were shown. A similar analysis will be made with the intensity, duration, severity, result and causal relationship.
- ✓ Although no safety hypotheses are established, nor is it taken into account for the estimation of the sample size, stopping the study was considered if serious adverse events that threatened the patient's life were detected in the combined sample of both populations, with association of causality with the vaccine under study, and in a magnitude greater than 5% of the participating subjects.

►Immunological evaluation:

Satisfactory Immune Response not defined; the immunological studies that were carried out will contribute to define it for the subsequent studies.

Seroconversion (According to the level of IgG anti-RBD antibodies reached 28 days after the dose used compared to pre-vaccination levels):

- ✓ Estimate the 95% confidence interval.
- ✓ Active virus neutralizing antibody titer:
- ✓ The geometric mean of the antibody titers was estimated, with the associated 95% confidence interval.
- ✓ Pre- and post-vaccination values were compared using the Student's t-test or the Mann-Whitney U-test (with the logarithmically transformed variable), depending on the assumption of approximation of the data to a normal distribution.
- ✓ Correlation between neutralizing antibody titers and IgG antibody levels, % RBD:ACE2 inhibition, and 50 inhibitory titer was estimated using Pearson's correlation coefficient or Spearman's correlation coefficient (in case of no approximation of the data to a normal distribution).

IgG antibody levels; Inhibition % of the RBD: ACE2 interaction in a dilution range from 1/100:

- Central trend measures estimated in every group, with their 95% confidence interval or the 25-75 percentile.
- Comparison among groups used the Student's-t test or the Mann-Whitney U test, depending on the data approximation to a normal distribution.

Determination of inhibitory titer 50 (TI50):

- ✓ Measures of central tendency were estimated with a 95% confidence interval.
- ✓ Pre- and post-vaccination values were compared using Student's t-test or Mann-Whitney's U-test (with logarithmically transformed variable), depending on the assumption of data approximation to a normal distribution.

►Procedures to diagnose and explain missing or extreme data (outliers)

For the diagnosis of aberrant or extreme data, the use of descriptive techniques (interquartile range) and graphics (boxplot and residual plots) was planned in the main response variables (Immunogenicity). The cases that were visually out of range would be analyzed with the Principal Investigator and later evaluated for possible influence on the results and conclusions, comparing the results of the analyzes with and without the detected value. If discrepancies were detected in the results of the two analyses, they would be reported and discussed in the statistical report and final report.

Missing data was handled as follows:

1. The proportion of volunteers who dropped out of the study was compared.

2. Whenever the data allows it, Kaplan Meier type graphs will be created to evaluate the pattern of dropouts.

3. Reasons for dropout would be described.

Missing values in the main safety or immunogenicity variables would be considered "missing at random (MAR)" and therefore ignored in the primary analysis. However, if more than 5% of all primary responses for all variables included in the primary analysis were reported as missing data, a

sensitivity analysis would be performed in addition to the primary MAR analysis. This sensitivity analysis would include an evaluation of the model results under the following assumptions:

1. Dragging the last observation (whenever possible).

2. Imputation for the worst case.

3. In the event that the start or end date of an adverse event was incomplete, it would be imputed by the worst possible case.

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2. Imputation for the worst case.

3. In the event that the start or end date of an adverse event was incomplete, it would be imputed by the worst possible case.

7.7.2 Sample-size determination

A formal calculation of the sample size was not performed as it was an exploratory study. Their results will serve as the basis for building hypotheses to be confirmed in future studies with this vaccine. The two populations studied are defined a-priori. It was planned that they would be made up of:

1) Up to 30 convalescents from COVID-19 from Italy, of both sexes, with a mild or moderate clinical picture of COVID-19 and aged between 19-59 years and after 2 months of being discharged with PCR or TRA negative. Ultimately, this group did not participate in the study, as will be described in Chapter 9.

2) Up to 30 volunteers from Italy, apparently healthy, of both sexes, aged between 19-59 years old, with no history of having suffered from COVID-19, and vaccinated against SARS-CoV-2 between 3 and 12 months before the start of the study.

7.7.3 Data collection and handling

The Management System for clinical studies "OpenClinica" in its Community version was used. The Clinical History, the Data Collection Notebook and the Adverse Events Diary are electronic. The first two were accessible to Spanish and Italian speaking specialists, through automatic translation programs. The Adverse Event Diary in Italian with automatic translation for Spanish-speaking specialists.

Every time the Electronic Medical Record was updated, with the data collected from the volunteer's interview, his physical examination, the data from the adverse event diary, as well as the results of the laboratory studies, the research doctor filled out the CRD email with the relevant data. The specialists of the clinical sites in Cuba and Italy in charge of these procedures had access to the use of these documents, as well as the information that was generated.

These activities were advised by specialists in Data Management, as established in the work procedures.

The data cleaning was carried out by the Data Management team, through an exhaustive review of the documentation, with the aim of detecting and eliminating corrupt or inaccurate records, in case of incorrect, incomplete or inaccurate information. This team managed to correct the erroneous or inaccurate data and replace it with the corresponding information, after analyzing it with the research team.

The Data Management Department was responsible for the electronic file. The electronic Medical Record and CRD were available for review during the Quality Control visits to the clinical site in Cuba, carried out by the IFV Quality Assurance Directorate and the CENCEC monitors and auditors; as well as the inspections carried out by CECMED specialists. Similarly, they could be reviewed during the conduct of the trial in Italy.

7.7.4 Change in th study's conduction or in the planned analysis

Due to logistical difficulties at the "Amedeo di Savoia" Hospital Laboratory, it was not possible to perform the viral neutralization test with all the planned SARS-CoV-2 variants of interest (D614G, alpha, beta, delta) in this institution; only the beta and delta variants were studied in Italy.

For this reason, the evaluation of live virus neutralizing antibodies was complemented at the Cuban Civil Defense Laboratory, with experience in other clinical studies with vaccines of the "Sovereign" series. On the other hand, considering the emergence of omicron and the availability of serum, this variant was included and alpha was not evaluated. Taking into account that the techniques differ between laboratories and to facilitate the comparison of the results, the beta and delta variants were re-evaluated, so they were studied in Cuba by the viral neutralization test: D614G, beta, delta and omicron .

Analyzes were performed as planned except:

- The analyzes corresponding to the variants of interest are included with the determinations made in the Cuban Civil Defense Laboratory.

- Immunogenicity analyzes are carried out according to the vaccination platform in order to evaluate future hypotheses about the vaccine-specific booster capacity.

8 PARTICIPATING SUBJECTS

8.1 Subjects' disposition

The pre-selection of the subjects was carried out by the designated Clinical Investigators in Italy. In Cuba, the final recruitment and inclusion of the volunteers was carried out, followed by vaccination.

In Italy, the clinical trial is announced using social networks and websites, organized by AICEC (Agency for Economic and Cultural Exchange with Cuba). The information included all the data concerning the Selection of the Subjects. Interested parties had to fill out an electronic form. The data was analyzed by the Italian Researchers, a process that was controlled by the Principal Investigator and the Promoter Researcher in Cuba.

Twenty convalescents and 188 subjects previously immunized with other vaccines were enrolled.

Of the 20 convalescents, 3 were excluded in Italy for not meeting any selection criteria; 14 declined to participate as they could not travel on the scheduled date. Finally, 3 convalescents arrived in Cuba, all of them excluded for having suffered from COVID-19 less than 2 months before the start of the trial.

Of the 188 subjects previously immunized with mRNA or viral vector vaccines, 98 were excluded in Italy for not meeting any selection criteria. Of the remaining, 60 decided not to participate, since they could not travel on the planned date. Finally 30 convalescents arrived in Cuba, all were initially included and vaccinated. During the process of filling out the CRDs, it was found that one of the participants had been incorrectly included, since he had been vaccinated with another vaccine before the minimum 3 months established according to the protocol, so he was included in the ITT analysis.

See Figure 3 and ANNEX 7.

8.2 Protocol deviations

Tests to assess safety and planned tests to assess immunity were performed as established. The only deviation detected was the misincluded volunteer, described in 9.1, who completed the study and whose results were analyzed as planned.

As we pointed out in 8.7.4, due to logistical difficulties in the "Amedeo di Savoia" Hospital Laboratory, the viral neutralization test against all the planned SARS-CoV-2 variants of interest could not be performed in this institution. so it was decided to complement the study at the Cuban Civil Defense Laboratory. On the other hand, considering the emergence of omicron and the availability of serum,

this variant was included and alpha was not evaluated. Finally, the following were studied: D614G, beta, delta and omicron.

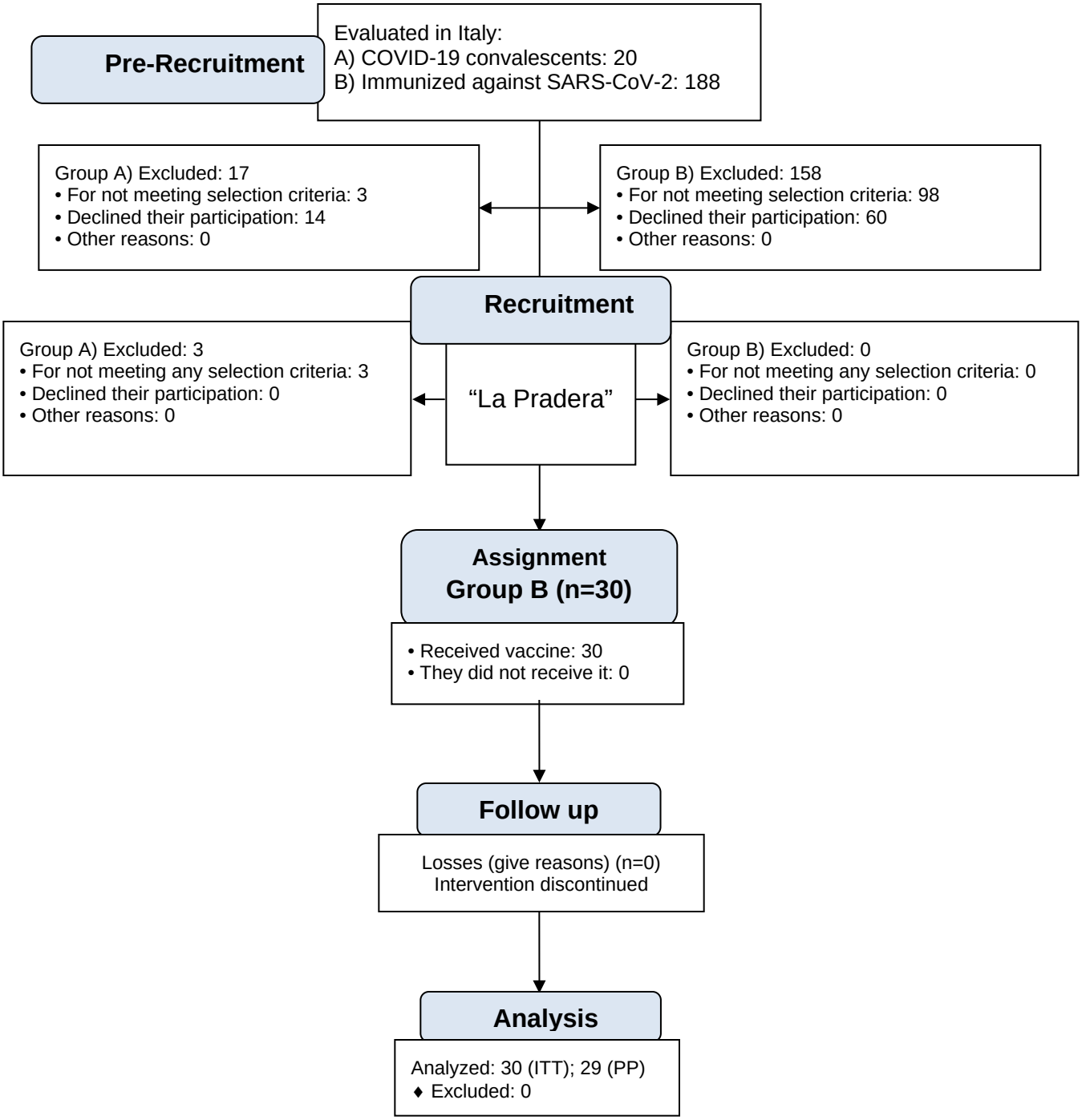

Fig. 3. Subjects disposition. Flow Diagram.

9 ASSESSMENT OF IMMUNOGENICITY (EFFICACY)

9.1 Analyzed data sets

The 30 subjects considered are included in this report. Efficacy analyzes were performed in the Per Protocol (PP) population, with the available determinations, and in the Intention to Treat (ITT) population. The safety analysis was performed on the ITT population that matches the safety population. A poorly included subject, with a time since vaccination of less than 3 months, is excluded from the immunogenicity analyzes of the PP population.

9.2 Demographics and other baseline characteristics

Demographic characteristics are summarized in Table 8. A higher proportion of men (73.3%), of subjects with white skin color (96.7%), mean age of 39.6 years, varying between 25 and 59 years and BMI around of 25 kg/m2. The demographic characteristics of all included subjects are listed in Annex 16.7.4.

Table 8. Demographic and Base Variables

	SOBERANA® Plus
N	30
Sex	
Feminine	8 (26.7%)
Male	22 (73.3%)
skin color _	
White	29 (96.7%)
mestizo	1 (3.3%)
Age (years)	
Half of)	39.6 (8.5)
Median (IQR)	38.5 (12.0)
Range	(25; 59)
Weight (kg)	
Half of)	74.7 (13.7)
Median (IQR)	72.0 (17.8)
Range	(45.0; 108.0)
Size (cm)	
Half of)	172.2 (8.5)
Median (IQR)	170.0 (12.9)
Range	(155; 187)
BMI (kg/ m^2)	
Half of)	24.6 (3.6)
Median (IQR)	24.9 (5.5)
Range	(18.7; 33.5)

SD: Standard desviation¸ IR: Intercualtilic range

70% of the included subjects had been immunized with the Pfizer vaccine and a total of 23 subjects (76.7%) with the mRNA platform. The time from the end of vaccination had a median of 4 months, Table 9. In a subject vaccinated with Johnson & Johnson, the time from vaccination was 2 months, which was detected after the inclusion and administration of the vaccine. This subject was considered poorly included and is analyzed within the Security and ITT population. Individual data is detailed in Annex 16.7.5

Table 9. Vaccination history

	SOBERANA® Plus		
N	30		
Vaccine received previously			
Pfizer- BioNtech	21 (70.0%)	mRNA	23 (76.7%)
modern	2 (6.7%)		
AstraZeneca	4 (13.3%)	Vectors viral	7 (23.3%)
Johnson&Johnson	3 (10.0%)		
Time since vaccination (months)			
Half of)	4.3 (1.7)		
Median (IQR)	4.0 (2.0)		
Range	(2; 9)*		

SD: Standard deviation; IQR: Interquartile range; * 1 subject (24-T) with time since vaccination with Johnson&Johnson less than 3 months (poorly included)

The use of some treatment prior to the start of immunization (Table 10) was reported by 4 subjects: 2 with allergies, 1 with psoriasis and 1 with bronchial asthma.

Table 6. Treatment prior to initiation of immunization

	SOBERANA® Plus	
N	30	**Drug**
with some treatment		
Yes	4 (13.3%)	
Nope	26 (86.7%)	
Reasons for treatment		
Allergy	2 (6.7%)	Hydrocortisone+Antihistamine ZYRTEC
bronchial asthma	1 (3.3%)	Beclomethazone+Montelukast
Psoriasis	1 (3.3%)	Calciprotriol+Betamethasone

Individual data is detailed in Annex 16.7.6.

9.3 Treatment Compliance Measurements

The study provided for the administration of a 50 µg dose of SOBERANA® Plus (d-RBD+ Aluminum Hydroxide Gel), via IM, volume 0.5 mL in the deltoid region. 100% of subjects received the planned doce

9.4 Efficacy Results and Tabulations of Individual Subject Data

9.4.1 Efficacy Analysis

The predicted variables to evaluate immunogenicity were: a) seroconversion according to the concentration of specific anti-RBD IgG antibodies and b) concentration of specific anti-RBD IgG antibodies, c) neutralizing antibody titer, d) % inhibition of ACE2 and e) ID 50 : Serum dilution that inhibits 50% of the interaction between RBD and ACE2.

Table 11 shows the results relative to the concentration of IgG anti-RBD antibodies in the Intention to Treat (ITT) population and in the Per Protocol (PP) population. As can be seen, 80% and 79.3% seroconversion is reached in both populations, respectively, and more than 60% seroconversion can be expected with 95% confidence. Regarding the concentration of antibodies, statistically significant increases are detected at 28 days compared to pre-vaccination values, Figure 4 (PP).

Table 7. Anti-RBD IgG antibody concentration.

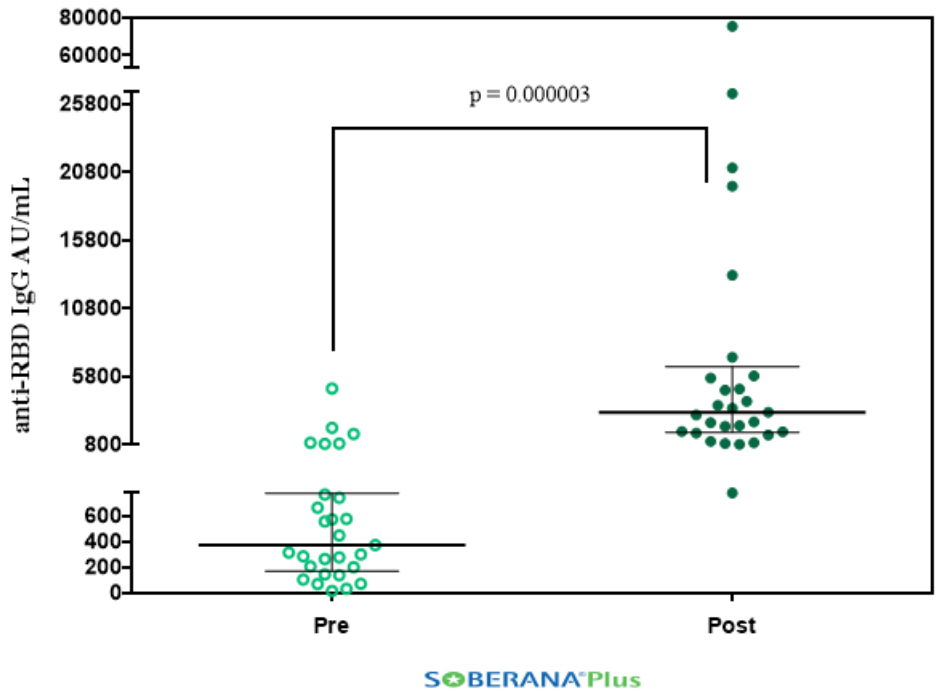

Fig. 4. Anti-RBD IgG antibody concentration after 1 dose of SOBERANA® Plus (PP population).

Quantification of molecular neutralization (mVNT) shows an estimated 12-fold increase in both study populations (Table 12), with a lower limit of the 95% CI for the ratio greater than 7.5, Figure 5. The % inhibition of the RBD:ACE2 interaction also shows a significant increase at 28 days with a median inhibition greater than 90% (Figure 5).

Table 8. Inhibitory titre of RBD:ACE2 interaction

			SOBERANA® Plus	
			ITT	PP
		N	30	29
mVNT $_{50}$	0	MGT	147.3	160.4
		CI 95%	(84.8; 255.9)	(93.1; 276.1)
	28 days	MGT	1830.1	1995.5
		CI 95%	(1119.2; 2992.8)	(1240.0; 3211.1)
	p(Student t)		2.2048E-11	7.0707E-11
	Ratio (95% CI)		12.4 (7.6; 20.3)	12.4 (7.5; 20.7)
% Inh RBD:ACE 2	0	Median	60.5	61.2
		Percentiles 25-75	(46.2; 84.9)	(49.0; 85.5)
		Range	(9.8; 94.3)	(12.9; 94.3)
	28 days	Median	91.6	91.6
		Percentiles 25-75	(89.9; 92.4)	(90.1; 92.5)
		Range	(65.5; 94.3)	(80.4; 94.3)
	p (Wilcoxon)		0.000004	0.000007

mVNT $_{50}$ = dilution that inhibits 50% of the RBD:ACE 2 interaction or molecular neutralization titer. GMT=Geometric Mean Molecular Neutralization Titers; 95% CI: Confidence interval at 95%; Ratio: Post/Pre Ratio (95% CI for Ratio); % Inh RBD:ACE 2 at 1/100 serum dilution

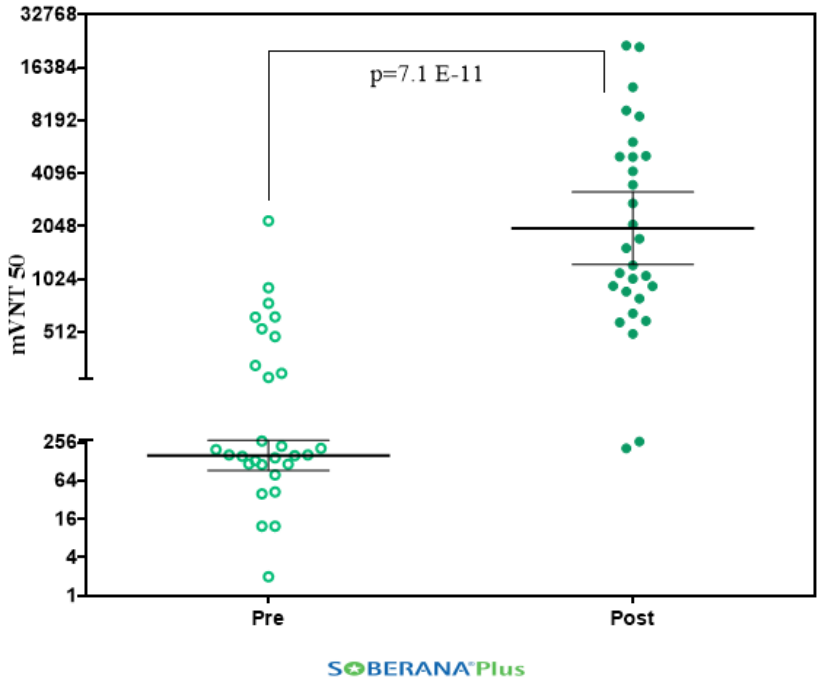

Fig. 5. Molecular neutralization titer (mVNT) after 1 dose of SOBERANA Plus (PP Population)

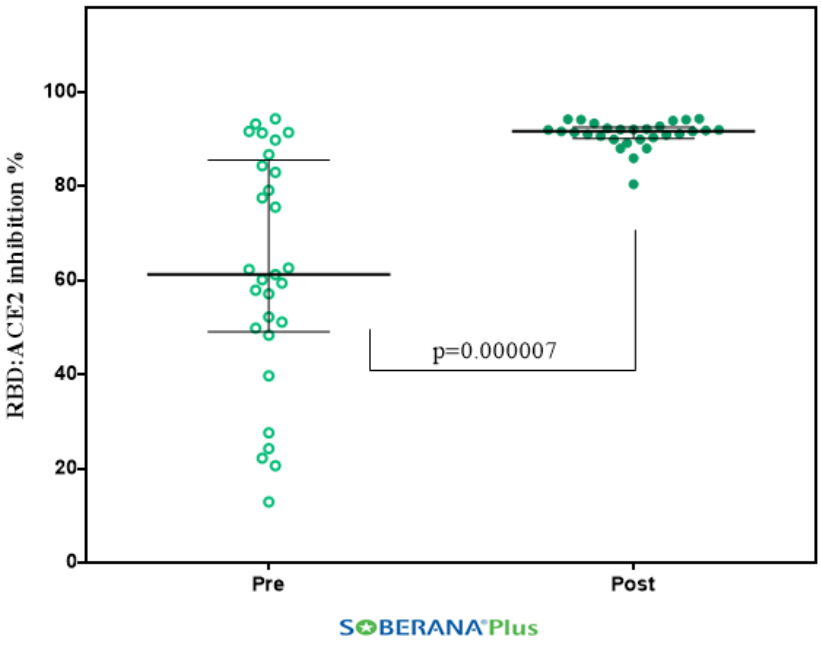

Fig. 6. % Inhibition of RBD:ACE2 after 1 dose of SOBERANA Plus (PP Population)

Table 13 shows the results of viral neutralization (cVNT) performed in Italy against SARS-CoV-2 delta and beta variant before vaccination with SOBERANA® Plus and at 28 days. Significantly higher values are detected at 28 days for both variants. For the delta variant, an increase ratio of 9 units is estimated in both populations and greater than 6 units of magnitude with a confidence of 95%. For the beta variant, the rate of increase is greater than 5 units; greater than 3 units with a confidence of 95% (Table 13, Figure 7). Neutralization against the beta variant is significantly lower than neutralization against the delta variant, with a 2.5-fold decrease ratio (Figure 7).

Table 9. Viral neutralization carried out in Italy against the delta and beta variants of SARS-CoV-2

			SOBERANA® Plus	
			ITT	PP
		N	30	29
cNTV delta variant	0	MGT	7.7	7.8
		CI 95%	(6.0; 10.0)	(6.0; 10.3)
	28 days	MGT	71.9	76.2
		CI 95%	(43.6; 118.6)	(46.1; 126.2)
	p(Student t)		1.7345E-10	2.303E-10
	Ratio (95% CI)		9.3 (5.8; 14.9)	9.7 (6.0; 15.7)
cNTV beta variant	0	MGT	5.3	5.3
		CI 95%	(4.7; 5.9)	(4.7; 5.9)
	28 days	MGT	28.8	30.5
		CI 95%	(16.8; 49.2)	(17.8; 52.5)
	p(Student t)		2.2544E-7	1.6668E-7
	Ratio (95% CI)		5.4 (3.2; 9.1)	5.8 (3.4; 9.7)

cVNT = conventional viral neutralization titer. MGT=Geometric Mean of Neutralization Titles; 95% CI: Confidence interval at 95%

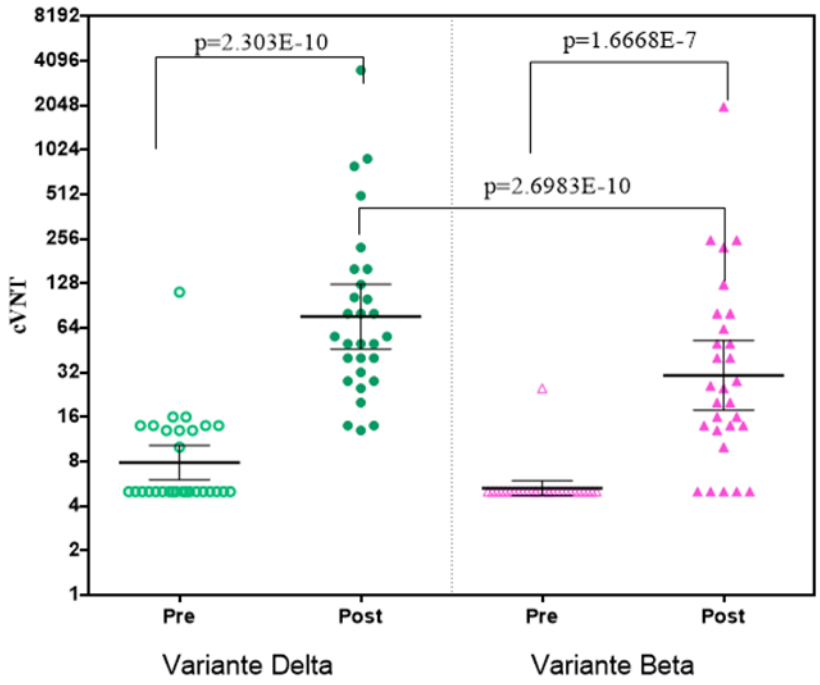

Fig. 7. Viral neutralization after 1 dose of SOBERANA® Plus (PP Population)

Bivariate correlations between immunogenicity variables at 28 days are shown in Table 14. Significant correlations are detected between all pairs of variables (except between mVNT and % Inhibition). However, correlation coefficients greater than 0.7 are only observed between molecular neutralization (mVNT) and the concentration of anti-RBD IGG antibodies (Anti-RBD IgG UA/mL) and between cVNT (in both variants of interest) with respect to the antibody concentration and molecular neutralization. A high linear correlation between the neutralization against both variants is also detected.

Table 10. Bivariate correlations between Immunogenicity variables at 28 days.

	Anti-RBD IgG UA/mL	% Inh RBD:ACE 2	mVNT $_{50}$		
SOBE-RANA Plus	**Anti-RBD IgG UA/mL**	r ^{2} Spearman	1,000		
		p	.		
		N	29		
	% Inh RBD:ACE 2	r ^{2} Spearman	0.493	1,000	
		p	0.007	.	
		N	29	29	
	mVNT $_{50}$	r ^{2} Spearman	0.926	0.300	1,000
		p	0.000	0.114	.
		N	29	29	29
	cNTV	r ^{2} Spearman	0.912 **	0.455	0.892
		p	0.000	0.013	0.000
		N	29	29	29

Table 15 shows the results of viral neutralization (cVNT) against the DG614, delta, beta and omicron variant carried out at the Cuban Civil Defense Laboratory. Significantly higher values are detected at 28 days for all variants. No significant differences are detected at 28 days between the DG614, delta and omicron variants; neutralization values against beta are significantly lower than the rest of the variants of interest (Figure 8).

Table 15. Viral neutralization of variants of interest (Civil Defense Laboratory of Cuba)

	DG614		Beta		Delta		Omicron	
	T0	T28	T0	T28	T0	T28	T0	T28
GMT	36.7	440.4	5.7	112.4	14.2	409.9	25.4	619.2
LI 95%	25.0	285.4	3.9	64.2	9.0	247.5	17.8	326.2
LS 95%	53.8	679.5	8.3	196.7	22.1	678.8	36.2	1175.5
	7.2833E-12		3.8727E-13		9.2574E-13		3.3583E-12	
	12.0 (7.6; 19.1)		19.8 (12.1; 32.4)		28.9 (16.3; 51.4)		24.4 (13.7; 43.4)	

LI: Lower Limit of the 95% CI; LS: Upper limit of the 95% CI

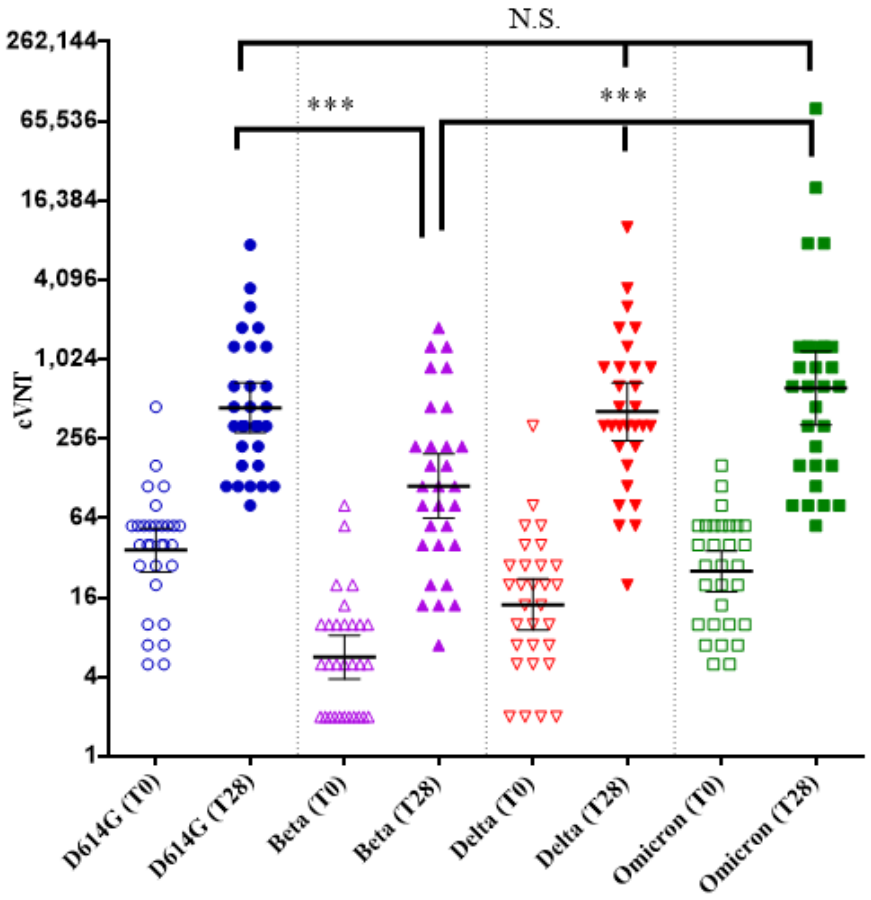

Fig. 8. Viral neutralization after 1 dose of SOBERANA® Plus in 4 variants of interest

9.4.2 Analytical/Statistical Topics

All planned analyzes were performed. This is an exploratory study that did not formally set out to answer statistical hypotheses, although paired hypothesis tests were planned and performed to explore changes after vaccination.

9.4.3 Adjustment for covariates

No adjustment for covariates was planned as it was an exploratory study. However, in order to evaluate future hypotheses about vaccine-specific boosting capacity, immunogenicity results by platform are shown in Figure 9, taking into account the small sample size of each vaccine specifically

(except Pfizer). Although the pre-post comparisons and at each time between the platforms are incorporated, they are biased by the imbalance in the sample sizes for each one.

However, for both platforms significant increases in IgG, % inhibition mVNT and cVNT (delta variant evaluated in Italy) are detected. On the other hand, the levels of IgG and % of inhibition are smaller for the subjects vaccinated with viral vectors, from the moment before vaccination and after the administration of SOBERANA Plus; No differences in molecular or viral neutralization were detected between the vaccination platforms.

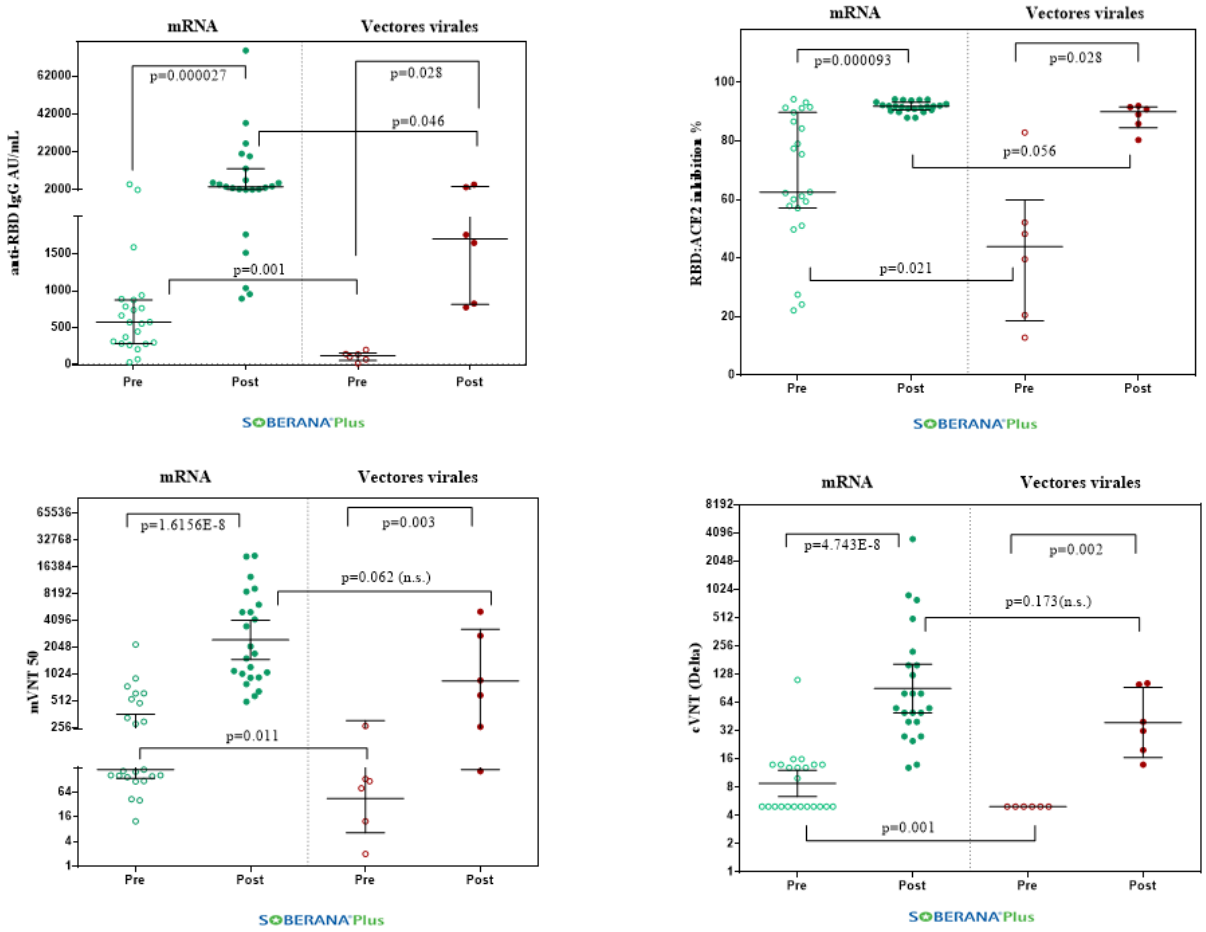

Fig. 9. Immunogenicity according to Previous Vaccination Platform (PP Population)

According to the viral neutralization of the variants of interest, significant increases are detected over time for both platforms. Prior to vaccination with Soberana-plus, lower viral neutralization values are detected for the viral vector platform (except with the delta variant). After vaccination with Soberana-

plus, no differences in viral neutralization were detected between the vaccination platforms for any of the variants of interest. (Figure 10).

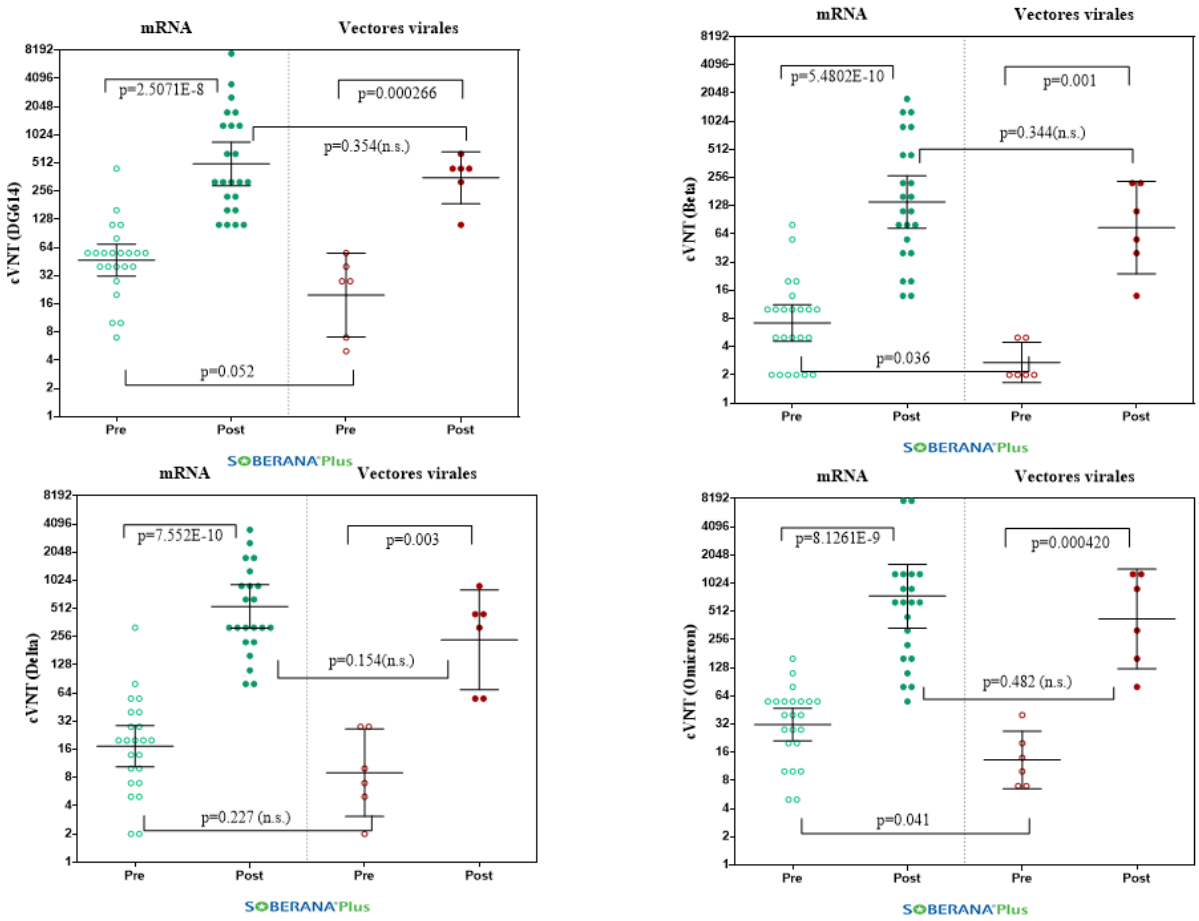

Fig. 10. Viral neutralization by Platforms in the 4 variants of interest studied at the Cuban Civil Defense Laboratory

For subjects previously immunized with 2 doses of the Pfizer-BioNtech vaccine, significant increases were detected in all immunological variables, with an increase ratio in cVNT for the delta variant (Italy Laboratory) estimated at 10.2 units (95% CI: 5.3; 19.6) (Figure 11).

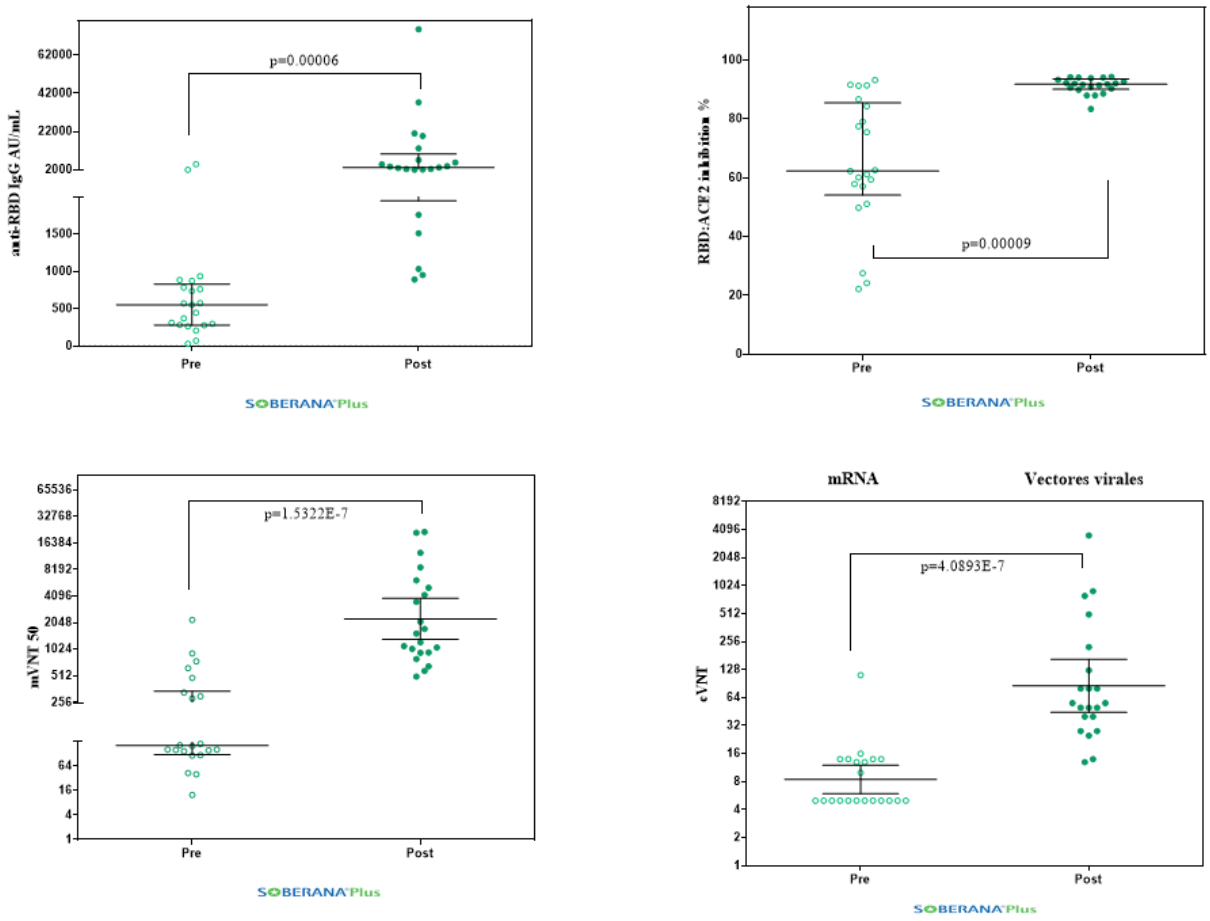

Fig. 11. Immunogenicity for subjects previously immunized with the Pfizer-BioNtech vaccine (PP population)

Individual data is detailed in Annex 16.7.7.

9.4.4 Handling dropouts and missing data

No dropouts or missing data occurred for any of the variables considered.

9.4.5 10.4.5 Interim Analysis and Data Monitoring

The planned intermediate analyzes were carried out by the Independent Data Monitoring Committee (IDMC) for the safety evaluation of the vaccine candidate and the immunogenicity results were controlled. They verified the safety of the vaccine and its low reactogenicity.

9.4.6 Drug-Disease and Drug-Drug Interactions

Concomitant medication use is summarized in Table 15. Some treatment was used in 3 subjects, all to treat some adverse event (100% of mild intensity, A4 causal HTN and the other 2 inconsistent with vaccination and lasting less than or equal to 24 hours); the 3 drugs were used in a single dose.

Table 15. Concomitant treatments.

Treatment concomitant		**SOBERANA® Plus**
	N	30
with some treatment	Yes	3 (10.0%)
	Nope	27 (90.0%)
Event Adverse	Drug	
AHT	Captopril	1 (3.3%)
general malaise	Dipyrone	1 (3.3%)
Muscle contracture in the neck	Diclofenac	1 (3.3%)

The individual data of the concomitant treatments are detailed in Annex 16.7.8.

9.4.7 Efficacy conclusions

The vaccine demonstrated its immunogenicity. The live virus neutralization test was very high against all variants tested. The other immunological variables evaluated were significantly increased by vaccination. We can affirm that SOBERANA® Plus ST increased the immune response against the RBD of SARS-CoV-2; much higher than prevaccinal levels.

10 SAFETY ASSESSMENT. ADVERSE EVENTS

10.1 Degree of Exposure

The study established a treatment exposure time of up to 28 days (one administration).

10.2 Adverse Events

10.2.1 Brief Summary of Adverse Events

Adverse events (AEs) that occurred since administration were reported in the analyzed population. In the population of 30 subjects, 36.7% of the subjects treated with the candidate under study reported an AE. There were 16 adverse events of 6 different types, all of mild intensity, 68.8% requested and 81.3% consistent with vaccination. Most are reported in the first 24 hours and last less than 24 hours. No serious or severe adverse event (SAE) occurred (Table 17).

Table 17. Summary of adverse events.

Categories by patients and AE	SOBERANA® Plus
N	30
Subjects with at least one AE	11 (36.7%)
Subjects with any treatment-related AE	11 (36.7%)
Subjects with some severe AE	0
Subjects with any serious treatment-related AEs	0
Subjects with some severe AE	0
Subjects with any severe AEs related to treatment	0
EA	**16**
Treatment-related AEs	13 (81.3%)
serious AEs	0
Treatment-related serious AEs	0
severe AEs	0
Treatment-related severe AEs	0

10.2.2 Analysis of Adverse Events

Table 18 identifies the frequency of each event observed by Intensity and Causality, specifying in each case the inclusion number that each one refers to.

Table 18. Adverse events: number observed and rate, with patient identification

	Mild		**Total**
	R	NR	R+NR
Muscle contracture in the neck		1 (3.3%) 27-T	1 (3.3%)
Pain	11 (36.7%) 01-T, 02-T, 03-T, 06-T, 07-T, 14-T, 15-T, 17-T, 22-T, 27-T, 29-T		11 (36.7%)
sore throat		1 (3.3%) 14-T	1 (3.3%)
general malaise		1 (3.3%) 14-T	1 (3.3%)
Arterial hypertension	1 (3.3%) 07-T		1 (3.3%)
Itching at the vaccination site	1 (3.3%) 07-T		1 (3.3%)

The frequency of subjects with each AE was summarized in Table 19. Solicited and local pain was present at the injection site (36.7%), all consistent with vaccination. There were no solicited systemic events. The rest of the events were unsolicited, one subject with pruritus at the vaccination site (classified as a local type adverse event), and systemic type, only one subject with sore throat and general malaise, one subject with contracture in the neck and a subject with arterial hypertension (classified as A4).

Table 19. Frequency of subjects with each adverse event

	System	EA	SOBERANA® Plus
			30
Requested	Local	Pain*	11 (36.7%)
Unsolicited	Local	Itching at the vaccination site*	1 (3.3%)
	systemic	Muscle contracture in the neck	1 (3.3%)
		Throat pain	1 (3.3%)
		Arterial hypertension**	1 (3.3%)
		General discomfort	1 (3.3%)

* Causality A1; ** Causality A4

The global characterization of adverse events is shown in Table 20. 100% of the events were of mild intensity. There were no related SAEs. All events were fully recovered. More than 80% of the reported events were classified as consistent with vaccination. 75% of the reported events were local. 68.8% were requested. They appeared fundamentally in the first 24 hours and mostly lasted less than 24 hours (56.3%).

Table 20. Global characterization of adverse events

Overall characterization		SOVEREIGN Plus	
		Freq .	%
Number of events adverse		16	100.0
Intensity	Mild	16	100.0
Gravity	Not Serious	16	100.0
Causality	Consistent with vaccination (1)	12	75.0
	Consistent with vaccination (4)	1	6.3
		AHT	
	Inconsistent with vaccination (C)	3	18.8
Result	Recovered	16	100.0
Guy	Local	12	75.0
	Systemic	4	25.0
Requested	Requested	11	68.8
	Unsolicited _	5	31.3

Overall characterization		SOVEREIGN Plus	
		Freq .	%
Number of events adverse		16	100.0
Appearance (hours)	≤ 60 minutes	1	6.3
	60 min-24 hours	12	75.0
	24-48 hours	0	0.0
	48-72 hours	1	6.3
	> 72 hours	2	12.5
Duration (hours)	≤ 24 hours	9	56.3
	24-48 hours	5	31.3
	48-72 hours	2	12.5
	> 72 hours	0	0.0

Table 21 describes the characterization of each reported adverse event.

Table 21. Characterization of each adverse event

		SOVEREIGN Plus	
Characterization		**Freq .**	**%**
Muscle contracture in the neck		1	100
Causality	C	1	100
Appearance	48-72h	1	100
Duration	≤ 24h	1	100
Pain		11	100
Causality	A1	11	100
Appearance	60min-24h	11	100
Duration	≤ 24h	5	45.5
	24-48 hours	5	45.5
	48-72h	1	9.1
sore throat		1	100
Causality	C	1	100
Appearance	>72h	1	100
Duration	48-72h	1	100
high blood pressure		1	100
Causality	A4	1	100
Appearance	60min-24h	1	100
Duration	≤ 24h	1	100
general malaise		1	100
Causality	C	1	100
Appearance	>72h	1	100
Duration	≤ 24h	1	100
Itching at the vaccination site		1	100
Causality	A1	1	100
Appearance	≤60min	1	100

		SOVEREIGN Plus	
Characterization		**Freq .**	**%**
Duration	≤ 24h	1	100
100% of the AE were of Mild Intensity, Not serious and with Result completely resolved			

The individual data on adverse events are detailed in Appendix 16.7.9.

10.3 Serious Adverse Events

Serious adverse events do not occur.

10.4 Evaluation of the Clinical Laboratory

10.4.1 Evaluation of Each Laboratory Parameter

No blood chemistry, hematology, or other studies were performed to assess safety. Only rapid antigen tests for the diagnosis of SARS-CoV-2 and PCR were performed, as well as pregnancy tests where appropriate.

10.5 Safety Conclusions

SOBERANA® Plus vaccine is safe and well tolerated. No vaccine-related serious adverse events were detected. Adverse reactions were few; predominating the local ones and of slight moderate intensity. The frequency of adverse events associated with vaccination was 36.7%.

11 BENEFIT-RISK ANALYSIS

It was not planned in this study.

12 CONCLUSIONS

1. SOBERANA® Plus ST is safe and well tolerated. The frequency of subjects with adverse events associated with vaccination was only 37%. Adverse reactions were few; predominating the local ones and of slight intensity. No serious adverse events occurred.
2. A significant increase in neutralizing antibodies against live virus induced by vaccination against the SARS-CoV-2 variants studied was achieved.
3. The concentration of anti-RBD IgG antibodies, the seroconversion index, the percentage of RBD:ACE2 inhibition and the 50 inhibitory titer were markedly increased by vaccination compared to prevaccinal levels.

13 TABLES AND FIGURES OF THE STATISTICAL ANALYSIS NOT INCLUDED IN THE TEXT

Not planned

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15 ANNEXES

Annex 1: Clinical Trial Protocol.

Annex 2: Modifications to the Protocol.

Annex 3: Data Collection Notebook.

Annex 4: Information Sheet for the subject and Informed Consent.

Annex 5: Ethics and Review Committees.

Annex 6: Researchers and Centers.

Annex 7: List of patients.

Annex 8: Randomization scheme.

Annex 9: Audit certificates.Anexo 1: Protocolo de Ensayo Clínico.

Annex 10: Notification of Serious Adverse Events.

15.1 ANNEX 1. CLINICAL TRIAL PROTOCOL

Delivered to CECMED.

15.2 ANNXO 2. PROTOCOL MODIFICATIONS

No modification to the clinical trial protocol was requested from CECMED.

15.3 ANNEX 3. DATA COLLECTION NOTEBOOK

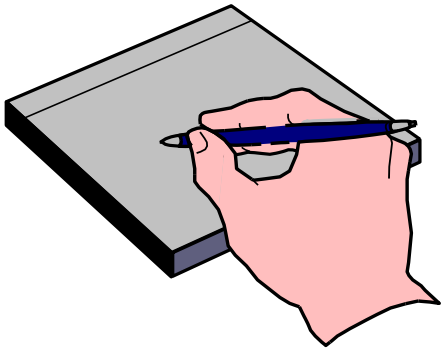
From the following pages:

DATA COLLECTION NOTEBOOK

"Exploratory study of the SOBERANA Plus ST vaccine, to evaluate its reactogenicity and immunogenicity in adults from Italy: convalescents from COVID-19, and in subjects with no history of this disease previously immunized against SARS-CoV-2"

IFV/COR/16

SOBERANA PLUS TURIN



Version: 1.0
October 2021

Clinical Site:|__||__|__| **Subject Identification Code:** |__|__|__| *(Inclusion Number)*

GENERAL DATA OF THE SUBJECT

1. **Date of Informed Consent:** |__|__|/|__|__|/|__|__| (*dd/mm/yy)*

2. **Subject Initials:** |__|__|__|__| *(capital letters)*

3. **Sex:** Feminine ❑1 Masculine ❑2

4. **Date of Birth:** |__|__|/|__|__|/|__|__| *(dd/mm/yy)* **5. Age:** |__|__| *(years old)*

6. **Skin Color:** White ❑1 Black ❑2 Mixed ❑3 Yellow ❑4

7. **Weight:** |__|__|__|,|__|__| *Kg* **8. Size:** |__|__|__|,|__| *cm* **9. BMI:** |__|__|,|__| *Kg/m2*

10. Convalescent from COVID-19: Yes ❑1 No ❑2 (*If the answer is negative, mark "No" and go to question 13. If the answer is positive, mark "Yes" and complete questions 11 and 12)*

11. Clinical form of COVID-19 *(If you answered "Yes" to question 10)***:**

Mild clinical picture❑1 Moderate clinical picture❑2

12. Date of discharge from hospital or home *(If you answered "Yes" to question 10)***:** |__|__|/|__|__|/|
|__| *(dd/mm/yy)*

13. Vaccination against COVID-19: Yes ❑1 No ❑2 (*If the answer is negative, mark "No" and go to question 16. If the answer is positive, mark "Yes" and complete questions 14 and 15)*

14. Vaccination date against COVID-19 *(If you answered "Yes" to question 13)***:**

First dose |__|__|/|__|__|/|__|__|*(dd/mm/yy)* / Second dose |__|__|/|__|__|/|__|__|*(dd/mm/yy)*

15. Vaccine Name: _____*(If you answered "Yes" to question 13)*

CURRENT TREATMENT, PRIOR TO THE START OF THE APPLICATION SCHEME OF SOBERANA PLUS ST

16. Does the subject receive any treatment?: Yes ❑ 1 Nope ❑ 2

№	Drug	Reason for medication	Frequency	Unit	Start date (dd /mm/ yy)	How long have you been using it
1			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
2			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
3			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
4			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
5			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
6			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
7			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
8			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
9			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
10			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3
11			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days ☐ 1 months ☐ 2 years ☐ 3

Unit : 1. µg; 2. mg; 3.G; 4. MU; 5. AU; 6. mL ; 7. Others: _____; 8. Others: _____; 9. Others: _____
Frequency : 1. Daily; 2. Twice a week; 3. Three times a week; 4. every 2 hours; 5. every 3 hours; 6. every 4 hours; 7. every 6 hours; 8. every 8 hours; 9. every 12 hours; 10. Other: _____; 11. Other: _____; 12. Other: _____

CURRENT TREATMENT, PRIOR TO THE START OF THE APPLICATION SCHEME OF SOBERANA PLUS ST

№	Drug	Reason for medication	Frequency	Unit	Start date (dd /mm/ yy)	How long have you been using it
12			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
13			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
14			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
15			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
16			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
17			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
18			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
19			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
20			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
21			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3
22			|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| days □ 1 months □ 2 years □ 3

Unit : 1. µg; 2. mg; 3.G; 4. MU; 5. AU; 6. mL ; 7. Others: _____; 8. Others: _____; 9. Others: _____
Frequency : 1. Daily; 2. Twice a week; 3. Three times a week; 4. every 2 hours; 5. every 3 hours; 6. every 4 hours; 7. every 6 hours; 8. every 8 hours; 9. every 12 hours; 10. Other: _____; 11. Other: _____; 12. Other: _____

LABORATORY DETERMINATIONS PRIOR TO THE START OF THE APPLICATION SCHEME OF SOBERANA PLUS ST

17. Did the subject have a sample taken for PCR (or ART) and a pregnancy test (if applicable)?

Yes ❑1 Date: |__|__|/|__|__|/|__|__| *(dd/mm/yy)* **No** ❑2

18. Did the subject have a sample taken for the immunology laboratory? Yes ❑1 Date: |__|__|/|__|__|/|__|__| *(dd/mm/yy)* **No** ❑2

Determinations	Results
PCR or TRA for SARS-CoV-2	Neg □1 Posit □2
Pregnancy test	Neg □1 Posit □2 NA □3

Immunological Determinations	Results
Level of IgG anti-RBD	
% RBD:ACE2 inhibition at 1/100 dilution	
Inhibitory Title 50	
Neutralizing Antibody Titers. Variant: D614G	
Variant: Alfa	
Variant: Beta	
Variant: Delta	
Variant:	

VERIFICATION OF THE SELECTION CRITERIA

19. Is the application of the selection criteria and its analysis described in the Clinical History? Yes ❑1 No ❑2. (*In case of a negative answer, return to the case and record this moment in the Clinical History*)

20. Was the subject included in the study? Yes ❑1 No ❑2 **21. Inclusion date:** |__|__|/|__|__|/|__|__| *(dd/mm/yy)*

22. Inclusion Number: |__|__|

23. Age group to which he/she belongs: 19 – 59 years old ❑1

ADMINISTRATION OF THE VACCINE (A SINGLE DOSE WILL BE APPLIED)

24. Did the subject attend the consultation? Yes ❑1 **25. Consultation date:** |__|__|/|__|__|/|__|__| *(dd/mm/yy)*

26. Was the vaccine administered to the subject? Yes ❑1 Time: |__|__|:|__|__| *(hh:mm)* No ❑2

CONSULTATION CONTROL: Day 0;
Conclusion of the immediate observation to the application of SOBERANA PLUS ST

27. Were adverse events reported? Yes ❑1 (Complete the Adverse Events model) No ❑2

28. Was the use of new concomitant treatments reported? Yes ❑1 (*Completar el modelo de Tratamiento Concomitante*) No ❑2

29. Does the subject meet any of the study discontinuation criteria? Yes ❑1 (*completar el modelo de Interrupción y Conclusión del estudio*) No ❑2

CONTROL OFCONSULTATIONS

Consultations	**Was the consultation carried out?** (Yes, complete the rest of the questions. In case of a negative answer, leave the rest of the questions blank*)*		**Consultation date**	**Were adverse events reported?** (Positive answer complete the model of Adverse Events)		**Was the use of concomitant treatment reported?** (Positive answer complete the Concomitant Treatment model)		**Does the subject meet any of the study discontinuation criteria?** (Positive response complete the Study Conclusion model)	
	Yes	**No**		**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1st (Recruitment)	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑
2nd (Inclusion)	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑
1st day (after vaccination)	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑
2nd day	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑
3rd day	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑
Day 28	❑	❑	|__|__|/|__|__|/|__|__|	❑	❑	❑	❑	❑	❑

REQUESTED LOCAL ADVERSE EVENTS

30. Were any requested local adverse events recorded during the first 7 days? Yes ❑1 No ❑2

(In case of a negative answer, mark "No" and go to the next page. In case of a positive answer, complete the row of the Adverse Event that occurred and in the other events mark "No" in column A1)

A Adverse Event	A1 Does the AE occurred?		B Event start time and date *(dd/mm/yy) and (hh:mm)*	C End date and time of the event *(dd/mm/yy) and (hh:mm)*	E Intens.	F Serious Adverse Event? *If the answer is negative, column G is completed with∅*		G Serious Adverse Event due to:	H Result	I Causality
	Yes	No				Yes	No			
1 . Pain	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
2 . Erythema	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
3 . Volume increase	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
4 . Induration	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
5 . Local heat	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|

Legend

I: Intensity
1- Mild
2- Moderate
3- Severe

G: Serious Adverse Event due to:
1 -Requires hospitalization
2 -Prolongs current hospitalization
3 - Significant or persistent disability/incapacity results
4 - Life threatening
5 - Death

H: Re sul t
1 -Recovered
2 -Recovered with sequels
3 -Persists
4 -Death
5 -Unknown

I: Causality
A : Causal Association Consistent with Vaccination
B : Indeterminate
C : Causal association inconsistent with vaccination
D : Not Classifiable

EVENTS _ _ _ _ SYSTEMIC ADVERSE S _ _ _ _ REQUESTED _ _ _ _ _ _ _ _ _

31. Were any requested systemic adverse events recorded during the first 7 days? **Yes** ❑1 **No** ❑2 *(In case of negative answer, mark "No" and go to the next section. In case of positive answer, complete the row of the Adverse Event that occurred and in the others mark "No" in column A1)*

A Adverse Event	A1 Does the AE occurred?		B Event start time and date *(dd/mm/yy) and (hh:mm)*	C End date and time of the event *(dd/mm/yy) and (hh:mm)*	E Intens.	F Serious Adverse Event? *If the answer is negative, column G is completed with∅*		G Serious Adverse Event due to:	H Result	I Causality
	Yes	No				Yes	No			
6. Fever	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
7. General malaise	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|
8.Rash	❑1	❑2	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|__| / |__|__| / |__|__| |__|__| : |__|__|	|__|	❑1	❑2	|__|	|__|	|__|__|

Legend

I: Intensity
1- Mild
2- Moderate
3- Severe

G: Serious Adverse Event due to:
1 -Requires hospitalization
2 -Prolongs current hospitalization
3 - Significant or persistent disability/incapacity results
4 - Life threatening
5 - Death

H: Re sul t _
1 -Recovered
2 -Recovered with sequels
3 -Persists
4 -Death
5 -Unknown

I: Causality
A : Causal Association Consistent with Vaccination
B : Indeterminate
C : Causal association inconsistent with vaccination
D : Not Classifiable

OTHER EVENTS

32. Were any other adverse events recorded during the 28 days after vaccination? **Yes** ❑1 **No** ❑2

(In case of a negative answer, mark "No" and go to the next section. In case of a positive answer, complete the row of the Adverse Event)

A Adverse Event	B. Event start time and date *(dd/mm/yy) and (hh:mm)*	C End date and time of the event *(dd/mm/yy) and (hh:mm)*	D Requested Adverse Event?		E Intens.	F Serious Adverse Event? *If the answer is negative, column G is completed with∅*		G Serious Adverse Event due to:	H Result	I Causality
			Yes	No		Yes	No			
9.	|__|__| / |__|__| / |__| | |__|__| : |__|__|	|__|__| / |__|__| / |__| | |__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
10.	|__|__| / |__|__| / |__| | |__|__| : |__|__|	|__|__| / |__|__| / |__| | |__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
11.	|__|__| / |__|__| / |__| | |__|__| : |__|__|	|__|__| / |__|__| / |__| | |__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
12.	|__|__| / |__|__| / |__| | |__|__| : |__|__|	|__|__| / |__|__| / |__| | |__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
13.	|__|__| / |__|__| / |__| | |__|__| : |__|__|	|__|__| / |__|__| / |__| | |__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|

Legend

I: Intensity
1- Mild
2- Moderate

G: Serious Adverse Event due to:
1 -Requires hospitalization
2 -Prolongs current hospitalization

H: Re sul t _
1 -Recovered
2 -Recovered with sequels

I: Causality
A : Causal Association Consistent with Vaccination
B : Indeterminate

3- Severe	**3** - Significant or persistent disability/incapacity results **4** - Life threatening **5** - Death	**3** -Persists **4** -Death **5** -Unknown	**C** : Causal association inconsistent with vaccination **D** : Not Classifiable

OTHER EVENTS

A Adverse Event	B. Event start time and date *(dd/mm/yy) and (hh:mm)*	C End date and time of the event *(dd/mm/yy) and (hh:mm)*	D Requested Adverse Event?		E Intens.	F Serious Adverse Event? *If the answer is negative, column G is completed with∅*		G Serious Adverse Event due to:	H Result	I Causality
			Yes	No		Yes	No			
14.	|__|__| / |__|__| / |__|__|__| : |__|__|	|__|__| / |__|__| / |__|__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
15.	|__|__| / |__|__| / |__|__|__| : |__|__|	|__|__| / |__|__| / |__|__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
16.	|__|__| / |__|__| / |__|__|__| : |__|__|	|__|__| / |__|__| / |__|__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
17.	|__|__| / |__|__| / |__|__|__| : |__|__|	|__|__| / |__|__| / |__|__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|
18.	|__|__| / |__|__| / |__|__|__| : |__|__|	|__|__| / |__|__| / |__|__|__| : |__|__|	❑1	❑2	|__|	❑1	❑2	|__|	|__|	|__|__|

Legend

I: Intensity
1- Mild
2- Moderate
3- Severe

G: Serious Adverse Event due to:
1 -Requires hospitalization
2 -Prolongs current hospitalization
3 - Significant or persistent disability/incapacity results
4 - Life threatening
5 - Death

H: Re sul t _
1 -Recovered
2 -Recovered with sequels
3 -Persists
4 -Death
5 -Unknown

I: Causality
A : Causal Association Consistent with Vaccination
B : Indeterminate
C : Causal association inconsistent with vaccination
D : Not Classifiable

CONCOMITANT TREATMENT

33. Were concomitant treatments recorded during the 28 days after vaccination? **Yes** ❑1 **No** ❑2
(If the answer is negative, mark "No" and leave the table blank)

№	Drug	Reason for indication			Frequency	Unit	Start date	Finish date	Continue at the end of the period
		Treat AE	AE prophylaxis	Other *(specify)*					
1		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
2		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
3		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
4		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
5		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
6		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
7		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
8		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
9		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
10		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
11		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
12		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2
13		|__|__|	☐		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes ☐1 Nope ☐2

Treat AE : It is filled with the number of the adverse event. This number is located in the row where the EA is registered. **AE prophylaxis :** It is marked for those treatments that are indicated or administered to prevent AE. **Unit** : 1. µg; 2. mg; 3.G; 4. MU; 5. AU; 6.mL; 7. Others: _____; 8. Others: _____; 9. Others: _____

Frequency : 1. Daily; 2. Twice a week; 3. Three times a week; 4. every 2 hours; 5. every 3 hours; 6. every 4 hours; 7. every 6 hours; 8. every 8 hours; 9. every 12 hours; 10. Other: _____; 11. Other: _____; 12. Other: _____

CONCOMITANT TREATMENT

№	Drug	Reason for indication			Frequency	Unit	Start date	Finish date	Continue at the end of the period
		Treat AE	AE prophylaxis	Other *(specify)*					
14		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
15		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
16		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
17		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
18		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
19		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
20		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
21		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
22		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
23		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
24		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
25		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2
26		|__|__|	□		|__|__|	|__|	|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	Yes □1 Nope □2

Treat AE : It is filled with the number of the adverse event. This number is located in the row where the EA is registered. **AE prophylaxis :** It is marked for those treatments that are indicated or administered to prevent AE. **Unit** : 1. µg; 2. mg; 3.G; 4. MU; 5. AU; 6.mL; 7. Others: _____; 8. Others: _____; 9. Others: _____

Frequency : 1. Daily; 2. Twice a week; 3. Three times a week; 4. every 2 hours; 5. every 3 hours; 6. every 4 hours; 7. every 6 hours; 8. every 8 hours; 9. every 12 hours; 10. Other: _____; 11. Other: _____; 12. Other: _____

Clinical Site: |__||__| |__| **Subject Identification Code:** |__|__|__| *(Inclusion Number)*

SAMPLING AND LABORATORY DETERMINATIONS
DAY 28

34. Did the subject have a sample taken for lab. of immunology? **Yes** ❑1 Date: |__|__| / |__|__| / |__|__| *(dd/mm/yy)* **No** ❑2 **NPs** ❑3

Immunological Determinations	Results
Anti-RBD IgG level	
% RBD:ACE2 inhibition at 1/100 dilution	
Inhibitory Title 50	
Neutralizing Antibody Titers. Variant: D614G	
Variant: Alpha	
Variant: Beta	
Variant: Delta	
Variant:	

Clinical Site: |_|_|_| **Subject Identification Code:** |__|__|__| *(Inclusion Number)*

STUDY INTERRUPTION

This section will be completed for all subjects included in the study.

- For subjects who meet any interruption criteria, complete question 35 with “Yes”; select the cause(s) and proceed to complete the section "Conclusion of the Study"

35. Did the subject discontinue the study? Yes ❑1 No ❑2

(If yes, please mark the most appropriate category)

Interrupt Criteria	Yes	No
1- Voluntary abandonment.	□1	□2
2- Appearance of serious adverse event with causal relationship.	□1	□2
3- Subject who at any time during the study is PCR or TRA positive for SARS-CoV-2	□1	□2
4- Decision of the clinical investigator, based on changes in the patient's clinical status that justify stopping the volunteer's participation in the study.	□1	□2
5- Death of the subject	□1	□2
6- Other: Specify: _____	□1	□2

CONCLUSION OF THE STUDY

Indicate the study completion date for this subject.

Date:|__|__| / |__|__| / |__|__| *(dd/mm/yy)*

1.1 ANNEX 4: INFORMATION SHEET FOR THE SUBJECT AND INFORMED CONSENT.

Information sheet for the subject participating in the clinical study

Version 1.0

This document provides you with information about the objectives of this study and about the benefits and risks of participating in it.

We invite you to participate in this clinical study.

The medical specialists consider that you are eligible to be included in this study; however, your participation is a voluntary act. The researchers will explain to you orally and in writing the goals, benefits, and risks of this research. You need to know all the information before making the decision. You can take time to reflect, including talking to your family or another doctor.

General questions and answers about the study:

What is the title of the study?

"Exploratory study of the SOBERANA Plus ST vaccine, to evaluate its reactogenicity and immunogenicity in adults from Italy: convalescents from COVID-19, and in subjects with no history of this disease previously immunized against SARS-CoV-2".

Why is this study being done?

The global epidemiological situation caused by COVID-19 imposes the need to develop vaccines that prevent SARS-CoV-2 infection.

The emergence of new variants of the virus, such as delta and omicron, with high transmissibility, increase the risk of reinfection in convalescents from COVID-19, and that previously vaccinated individuals may become infected. For this reason, it has been suggested to boost immunity, in the case of convalescents by vaccination, and in individuals already vaccinated by adding a booster dose.

The Finlay Vaccine Institute has developed SOBERANA Plus ST that prevents the disease. The study that we propose is based on the successful clinical studies carried out in Cuban convalescents from COVID-19, as well as other studies in individuals vaccinated with two doses of vaccines against SARS-CoV-2, in which the notable increase in response was demonstrated. immune after a third dose with SOBERANA Plus ST. In all of them, the safety of the vaccine was demonstrated, as well as the high protection against SARS-CoV-2 achieved by most of the participants, including against different variants of the virus, as demonstrated at the " Amedeo di Savoy".

Is this study research?

Yes, an exploratory study is an investigation. The SOBERANA Plus ST vaccine has been authorized by the national regulatory authority of Cuba , and is used in mass vaccination campaigns carried out in this country. The proposed study aims to evaluate this vaccine in volunteers from Italy, convalescing from COVID-19 or previously vaccinated with another SARS-CoV-2 vaccine .

Who will participate in this study?

will be able to participate volunteers from Italy, of either sex, aged between 19-59 years, who are convalescing from COVID-19 or who have been previously vaccinated against this disease.

Who will not be included in this study?

You will not be included if you have any medical condition in a state of decompensation, among other causes, which will be analyzed and reported by the doctor who will evaluate you. The specialist doctor will inform you whether or not you meet the requirements to receive the SOBERANA Plus ST vaccine. On the other hand, even if you meet all the requirements to participate in the study, if the number of subjects is greater than planned, the selection to be included would be made by a random procedure.

What does the vaccine consist of?

It is a vaccine against SARS-CoV-2 that contains a fragment of one of its proteins, obtained by recombinant means; its use does not represent any risk of acquiring the disease. Unlike others that are applied in the world, this vaccine is not obtained from the inactivated virus or its genetic material.

What is the objective and the characteristics of the study?

The objective of the study is to demonstrate that SOBERANA Plus ST produces very few adverse events, and a high immune response, in volunteers from Italy, aged between 19 and 59 years, convalescing from mild and moderate COVID-19, as well as in individuals previously vaccinated with another SARS-CoV-2 vaccine.

How will the study be carried out?

- ✓ A doctor/clinic will explain all the features of the study, including the benefits and risks. You must provide your consent in writing to participate.
- ✓ You will be evaluated by doctors through a history, physical examination, polymerase chain reaction (PCR) test or Rapid Antigen Test (TRA) to diagnose SARS-CoV-2, and if necessary by other tests of lab to assess your health status.
- ✓ Vaccination consists of applying one dose (0.5 mL) of the vaccine intramuscularly in the arm.

- ✓ Once vaccinated, the patient will remain in the clinical site under medical observation for 1 hour, after which time the follow-up will continue on an outpatient basis.
- ✓ You will receive a model Adverse Event Diary, where you must collect all the information requested during the study.
- ✓ During the month that the study lasts, you will have 4 face-to-face consultations after vaccination, the designated doctors will communicate the dates of the post-vaccination consultations and other planned activities.

In order to evaluate the immune response induced by the vaccine, two 10 mL blood samples will be taken (before vaccination and 28 days after vaccination).

What benefits could participation in the study bring me?

The immunity acquired by the disease is not known exactly. Convalescents, as well as already vaccinated individuals, can become infected, especially when new variants of the virus circulate; so once vaccinated, you could be protected.

What benefits could the study provide for public health?

By proving that the vaccine is safe and protects against SARS-CoV-2 in the volunteers evaluated, it would advance to a higher phase in the investigation of this vaccine.

What are the drawbacks and discomforts of the study?

You may feel mild or moderate local and general discomfort after vaccination, similar to the effects caused by other vaccines, such as: pain, redness, induration of the area and general malaise. Also slight pain at the site of blood draws and slight discomfort from taking the sample for PCR or TRA. The follow-up that has been planned in the study, entails their transfer on a few occasions to the places planned for the corresponding consultations and exams.

What are the risks of participating in the study?

Very rarely serious adverse reactions may occur, such as anaphylaxis (type of allergic reaction) or other, for which specialized and immediate medical attention will be guaranteed.

In the event of an adverse event, how will I be treated?

If any adverse event appears during the observation time at the clinical site, the doctor will take the appropriate measures in the shortest possible time. In the very unlikely case of serious adverse events, the established medical emergency treatment protocols would be applied. At the end of the observation time after vaccination, the doctor will give you a Card that will identify you as a participant in the study, and if necessary, in the event of any event, you will show it at the Health Institution you go to.

What happens if I am harmed in the study?

In the exceptional case that you suffer any damage as a direct result of the study, the Health Systems that endorse the study will guarantee all the necessary medical care. In Cuba, his free treatment would be carried out at the "La Pradera" International Health Center or the "Cira García" Clinic, depending on the clinical picture. In Italy, the "Amedeo di Savoia" Hospital would be in charge of treating any adverse events that might arise.

Once inside the study, will it have any repercussion if I decide to leave it?

Your consent to participate in this study is voluntary. You may withdraw from it at any time.

How long will the study last?

You will be involved in this study for about a month, once you are included in the research.

Are there medications that can influence the results of the study?

During the 30 days before and after you are vaccinated, you should avoid receiving treatments with gamma globulin, steroids, or other drugs that affect response to the vaccine, of which you will be informed. Although the application of these drugs does not imply an additional risk, it should be reported to the investigator so that he can take it into account when evaluating the results of the study. In the event of any health situation that requires a specific medication, you must inform the study medical team.

What is my responsibility during the study?

You must comply with the vaccination schedule and all scheduled appointments. You will bring to them the Card that identifies you as a participant in the study. You must complete the Diary of Adverse Events that will be given to you and inform the researcher about diseases or medical events that occur after being included in this study, as well as any medication that is indicated.

Will my data be known during the study and publication of the results?

Your identity will be confidential, your data will be identified by a code and not by your name.

Are there reasons for the investigator to decide to discontinue participation in the study?

The researchers may withdraw you from the study for reasons such as: the appearance of a serious adverse event related to the vaccine, that your health condition decompensates or that you test positive for SARS-CoV-2.

Who to contact if you need information or report any event related to the study?

Dr. Vladimir Daniel Trujillo Machado, Principal Investigator, will be in charge of informing you of any event related to this study. If you have any concerns or questions, don't hesitate to contact him. The contact details are those indicated at the end of this document. When you are in Italy, you can contact Prof. Giovanni Di Perri, Head Researcher of the “Amedeo di Savoia” Hospital, by phone: 390114393828.

Dr. Vladimir Daniel Trujillo Machado
Main Investigator

International Health Center "La Pradera"
24h Guard Office:
Telephones, (53) 72725273; 72731441
Mobile: 53 52688447

INFORMED CONSENT FORM

The doctor Dr./Dr. _____ has informed me verbally and in writing about the study in which I will participate. It has given me an opportunity to reflect on my decision and I understand the information that has been provided to me.

I hereby voluntarily give my consent to participate in the study entitled:

"Exploratory study of the SOBERANA Plus ST vaccine, to evaluate its reactogenicity and immunogenicity in adults from Italy: convalescents from COVID-19, and in subjects with no history of this disease previously immunized against SARS-CoV-2 ".

I confirm that:

- ✓ I understand the benefits and risks of the study.
- ✓ I will know of any new information that may be of importance for my continuity in the study.
- ✓ I agree to comply with the vaccination and visits program, as well as to follow the instructions of those responsible for the study
- ✓ I will immediately report any changes that occur throughout the duration of the investigation.
- ✓ I agree to have blood drawn, take a sample for the PCR or Rapid Antigen Test to diagnose COVID-19, and the medical check-ups provided for in the study .
- ✓ I know that I can withdraw my consent to participate in the study at any time and that the doctor can decide my withdrawal depending on my health condition.
- ✓ I agree that the blood samples and data obtained may be used in this study.
- ✓ I consented for the medical information to be recorded and reviewed by the study staff while maintaining the confidentiality of my data.
- ✓ By signing this document, I voluntarily grant my consent to participate in the study and confirm that I have a copy of the "Informed Consent Form" in my possession.

Name and Surname of the Volunteer	Signature	Date/Time

Name and Surname of the Physician	Signature	Date/Time

15.4 ANNEX 5: ETHICS AND REVIEW COMMITTEES

Research Ethics Committee:

International Health Center "La Pradera", CUBA

Name and surname	Responsibility
Yanise Martinez Guerra	President
Janette Oliva Herrera	Vice president
Lourdes Rosa Hernandez List	Secretary
Dr. Armando Guerra Vilanova	Member
Daymis Rabeiro Gonzalez	Member
Ahmed Alvarez de Armas	Member
Dr. Abel Hernandez Perera	Member
Yamira Tellez Loredo	Member
Katia Garcia Mustelier	Community member

INTERAZIENDAL ETHICAL COMMITTEE
AOU CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO - AO ORDINE MAURIZIANO DI TORINO – ASL CITTÀ DI TORINO

Name and surname	Responsibility
Dr Marcello Maddalena	President
Prof. Paolo Cavallo Perin	Vice president
Dr. Mauro Alovisio	Secretary
Professor Luigi Biancone	Member
Prof. Francisco Giuseppe de Rosa	Member
Prof. Roberto Fantozzi	Member
Dr. Ivana Franchi	Member
Mr. Sergio Gaiotti	Representative member of the community
Dr. Mauro Giammarino	Member
Prof. Paolo Pieiro Limone	Member
Dr. Chiara Marengo	Member
Dr. Clara Merlini	Member
Dr. Elena Nave	Member
Prof. Barbara Pasini	Member
Prof. Dario Roccatello	Member
Prof. Renato Romagnoli	Member

Ing. Tommaso Agostino Sabbatini	Member
Prof. Sergio Sandrucci	Member
Dr. Elisa Sciorsci	Member
Dr. Marco Spada	Member
Dr. Lucia Tattoli	Member
Dr. Stefano Taraglio	Member

Independent Data Monitoring Committee (CIMD):

Name and surname	Formation	Responsibility	Location
Dr. Narciso Argelio Jiménes Pérez	1st Degree Specialist in Internal Medicine. Esp. 2nd Degree in Intensive and Emergency Medicine. MSc. in Infectology.	President	Institute of Tropical Medicine "Pedro Kourí" (IPK)
Dr. Mery Martinez Cabrera	1st Degree Specialist in MGI. MSc. in Satisfactory Longevity	Member	Directorate of International Relations of the MINSAP
Patricia Lorenzo-Luaces.	Degree in Mathematics. Masters in Mathematical Sciences	Member	Clinical Research. Molecular Immunology Center
Dr. Gisela Maria Suarez Formigo	First Degree Specialist in Immunology	Member	Clinical Immunology. Molecular Immunology Center

15.5 ANNEX 6: RESEARCHERS AND CENTERS

FINLAY VACCINE INSTITUTE

Name and Surname	Vocational training	Responsibility
Vicente Verez Bencomo phd	Phd in Chemical Sciences	Head of the COVID-19 Specific Vaccine Project
Yuri Valdes Balbin	Bachelor in Chemistry	Head of the COVID-19 Specific Vaccine Project
Dagmar Garcia Rivera phd	Phd in Pharmaceutical Sciences	Head of the COVID-19 Specific Vaccine Project
Dr. Rolando F. Ochoa Azze	Second Degree Specialist in Immunology. Dr.C. medical	Promoter Researcher
Yanet Climent Ruiz phd	Phd in Biological Sciences	Project manager
Fabrizio Chiodo phd	Phd in Applied Chemistry	Coordinating researcher in Italy
Raúl González Mugica	Bachelor in Biochemistry	Management of Data
Tech. Maite Medina	Computer Tech.	Data Operator
Marcos A. Fontaines	Bachelor in C. Pharmaceutical	Data Operator
Tech. Jennifer Espi Ávila	Computer Tech.	Data Operator
Tech. Yeney Domínguez Pentón	Computer Tech.	Data Operator
Marisel Martinez Perez	Bachelor in C. Pharmaceutical	Responsible for managing the SOBERANA Plus ST vaccine
Laura M. Rodríguez Noda	Bachelor in Microbiology	Responsible for immunological evaluations
Rocmira Perez Nicado	Biology	Immunological evaluations
Ismavy Castillo	Biology	Immune evaluations
Roberto Arias	Mathematics degree	Logistics and planning manager
Anais Linen Garcia	Computer science degree	Logistics and planning
Bertha Guillen Obregon	Chemical Engineer, MSc.	Quality assurance
Janet Lora Garcia	Pharmacy, Master in Science.	Quality assurance
Dr. Rodrigo F. Valera Fernandez	Microbiology Specialist	Sample handling
Aniurka Garces Hechavarria	Bachelor of Health Technology	Immunological evaluations
Tec. Aylín Amador Gómez	Tech. in Agronomy	Immunological evaluations
Tech. Yanet Rodríguez Estrada	Tech. in Industrial Pharmacy	Immunological evaluations
Indira Utria Torres	Degree in law and Master's in Law	Coordinator
Ricardo Perez Valerino	Bachelor of Nuclear Chemistry	Coordinator

MOLECULAR IMMUNOLOGY CENTER

Names and surnames	Vocational training	Responsibility
Belinda Sánchez Ramírez phd	Degree in Biochemistry, phd in Biology	Obtaining vaccine immunogen. Immunological evaluations
Tays Hernandez Garcia phd	Bachelor in Biochemistry, phd in Biology	Immunological evaluations
Ivette Orosa Vázquez	Degree in Biochemistry and Molecular Biology	Immunological evaluations
Marianniz Diaz Hernandez	Bachelor of Chemistry	Immunological evaluations

INTERNATIONAL HEALTH CENTER. "THE MEADOW" (CIS)

Names and surnames	Vocational training	Responsibility
Dr. Vladimir Daniel Trujillo Machado	Internal Medicine specialist. Diploma in Intensive Care.	Principal investigator
Dr. Nelly Cristina Valdivia Onega	Specialist in Health Administration, 2nd degree Specialist in Epidemiology and Public Health Organization and Administration	Research Physician
Dr. Marelys Castro Iglesias	Internal Medicine specialist	Research Physician
Dr. Ariel Gonzalez Lopez	Imaging Specialist	Research Physician
Dr. Loida Torres López	Clinical Laboratory Specialist	Research Physician
Dr. Janet Seoanes Piedra	Neurology Specialist	Research Physician
Dr. Danay Castro Iglesias	Internal Medicine specialist	Research Physician
Isumy Teresa Chuisent Gómez	Nursing degree. Master in Medical Emergencies	vaccinating nurse
Elizabeth de la Caridad Nodarse Amaya	Bachelor in Nursing.	Nurse
Ana Sofia Tamayo Taquechel	Bachelor in Nursing.	Nurse
Dianelis Suarez Revoll	Bachelor in Nursing	vaccinating nurse
Annia Abreu Godinez	Bachelor in Pharmacy	Responsible for managing the SOBERANA Plus ST vaccine
Nelia Hernandez Turiños	Agricultural Engineer. MSc.	Logistics and planning manager
Deysi Geli Gámez	Health Information Manager	Documentation Manager
Lourdes Hernández List	Degree in Psychology	Responsible for communication
Dr. Camilo Lenin Otero Motola	Internal Medicine specialist. Diploma in Intensive Care.	Research Physician
Ana Lourdes Artigas	Bachelor of Clinical Laboratory	Laboratory studies
Tech. Beatriz Álvarez Acevedo	Clinical Laboratory Tech.	Laboratory studies
Tech. Ibis Marlen Bermúdez Domínguez	Clinical Laboratory Tech.	Laboratory studies

NATIONAL COORDINATING CENTER FOR CLINICAL TRIALS (CENCEC)

Names and surnames	Vocational training	Responsibility
Pedro Pablo Guerra Chaviano	Master in Science in Clinical Trials	Responsible Monitor
Analeys R. Maceo Sinabele	Bachelor in Pharmaceutical C.	Display
Anabel Amador Gonzalez	Bachelor in Pharmaceutical C.	Display
Leani Martinez Garcia	Bachelor in Biology	Display

IMMUNOASSAY CENTER

Names and surnames	Vocational training	Responsibility
Irinia Y. Valdivia Alvarez phd	Graduate in Microbiology and phd in Healthcare	Immunological evaluations
Aurora Delahanty Fernandez	Bachelor and Master in Science in Biochemistry	Immunological evaluations
Darien Ortega Leon	Bachelor and Master in Science in Pharmaceutical Sciences	Immunological evaluations
Ariel Palenzuela Diaz	Bachelor and Master in Science in Biochemistry	Immunological evaluations

INSTITUTE OF CYBERNETICS, MATHEMATICS AND PHYSICS

Names and surnames	Vocational training	Responsibility
Carmen M. Valenzuela Silva	Bachelor and Master in Science in Mathematics	Responsible for Statistical Processing and Analysis

“AMEDEO DI SAVOIA” HOSPITAL (TORINO) ITALY

Names and surnames	Vocational training	Responsibility
Prof. Giovanni Di Perri	Medical	Researcher Responsible for the Clinical Site
Prof. Andrea Calcagno,	Medical	Sub-investigator
Dr. Mattia Giovanni Trunfio,	Medical	Sub-investigator
Dr. Valeria Ghisetti	Biology	Sub-investigator
Dr. Maria Grazia Milia	Biology	Laboratory studies
Dr. Rita Proia	Biology	Laboratory studies

15.6 ANNEX 7: LIST OF SUBJECTS

15.6.1 Registry of Included and Not Included

List of subjects evaluated in the CIS "La Pradera".

SCREENING NUMBER	AGE	INCLUDED AND EXCLUDED	CAUSE EXCLUSION
01-T	37	INCLUDED	
02-T	38	INCLUDED	
03-T	29	INCLUDED	
04-T	40	INCLUDED	
05-T	39	INCLUDED	
06-T	39	INCLUDED	
07-T	43	INCLUDED	
08-T	44	INCLUDED	
09-T	33	INCLUDED	
10-T	43	INCLUDED	
11-T	36	INCLUDED	
12-T	25	INCLUDED	
13-T	37	INCLUDED	
14-T	47	INCLUDED	
15-T	48	INCLUDED	
16-T	33	INCLUDED	
17-T	35	INCLUDED	
18-T	27	INCLUDED	
19-T	41	INCLUDED	
20-T	30	INCLUDED	
21-T	32	INCLUDED	
22-T	32	INCLUDED	
23-T	32	INCLUDED	
24-T	59	INCLUDED	NOTE- WRONG INCLUDED FOR HAVING BEEN VACCINATED AGAINST SARS-Cov-2 2 MONTHS IN ADVANCE
25-T	54	INCLUDED	
26-T	36	INCLUDED	
27-T	56	INCLUDED	
28-T	50	INCLUDED	
29-T	50	INCLUDED	
31-T	40	INCLUDED	

15.6.2 Discontinued Subjects

ID	treatment	Inclusion Date	Interruption Date	Cause of Interruption
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--	--	--	--	--
--	--	--	--	--

15.6.3 Subjects excluded from the efficacy analysis

ID	Treatment	Sex	Age	Observation	Reason(s)
24-T	SOBERANA PLUS	M	59	Was included by mistake, and was vaccinated	Have been vaccinated against SARS-CoV-2 two months before inclusion in the study

15.6.4 Demographics

Code	IC Signature	Initials	Sex	Age	Skin	Weight	Size	BMI
01-T	16-11-21	VA	M	37	White	95.1	182	28
02-T	16-11-21	MC	M	38	White	64.1	175	20
03-T	16-11-21	CI	F	29	White	62.69	166	22
04-T	16-11-21	FST	M	40	White	66.9	161	25
05-T	16-11-21	FB	M	39	White	69.46	169	24
06-T	16-11-21	AC	M	39	White	69.46	173	
07-T	16-11-21	PR	M	43	White	90	180	27
08-T	16-11-21	PM	M	44	White	65	157	26
09-T	16-11-21	AL	F	33	White	72	159	28
10-T	16-11-21	AP	M	43	White	70	180	21
11-T	16-11-21	GG	M	36	White	73.5	168.5	28
12-T	16-11-21	MV	F	25	White	63	164.5	
13-T	16-11-21	FM	M	37	White	72	167.5	25
14-T	16-11-21	SV	M	47	White	62	170	21
15-T	16-11-21	MV	M	48	White	76	170	26
16-T	16-11-21	IJES	F	33	Mixed	56	169	19
17-T	16-11-21	MS	M	36	White	79	173.5	26
18-T	16-11-21	AT	M	28	White	87.5	184	25
19-T	16-11-21	MC	M	41	White	89	181	27
20-T	15-11-21	BF	F	30	White	78	166	28
21-T	15-11-21	GR	M	32	White	78	179	24
22-T	16-11-21	H.H	F	32	White	60	175	19
23-T	16-11-21	MB	M	32	White	81	187	
24-T	16-11-21	FM	M	59	White	108	185	31

Code	IC Signature	Initials	Sex	Age	Skin	Weight	Size	BMI
25-T	16-11-21	PT	M	54	White	68.6	181	20.9
26-T	16-11-21	LV	F	36	White	45	155	18.7
27-T	16-11-21	GP	F	56	White	70.9	169	24.8
28-T	16-11-21	MA	M	50	White	76.8	169	23.7
29-T	16-11-21	RL	M	50	White	95.8	169	33.5
31-T	11-17-21	MMV	M	40	White	97	180	29

15.6.5 Vaccination history

StudySubjectID	Prevaccinated	FDose1	FDose2	Vaccine	FInclusion
01-T	Yes	05-21-21	01-07-21	Pfizer-BioNtech	16-11-21
02-T	Yes	09-06-21		Johnson&Johnson	16-11-21
03-T	Yes	16-06-21	07-21-21	Pfizer-BioNtech	16-11-21
04-T	Yes	27-02-21	05-18-21	AstraZeneca	16-11-21
05-T	Yes	06-23-21	07-28-21	Moderna	16-11-21
06-T	Yes	05-15-21	06-24-21	Pfizer-BioNtech	16-11-21
07-T	Yes	01-03-21	05-24-21	AstraZeneca	11-17-21
08-T	Yes	07-26-21	01-08-21	Pfizer-BioNtech	16-11-21
09-T	Yes	04-06-21	09-07-21	Pfizer-BioNtech	16-11-21
10-T	Yes	06-23-21	04-08-21	Pfizer-BioNtech	16-11-21
11-T	Yes	20-06-21	07-27-21	Pfizer-BioNtech	16-11-21
12-T	Yes	06-19-21	07-20-21	Pfizer-BioNtech	16-11-21
13-T	Yes	05-23-21		Johnson&Johnson	16-11-21
14-T	Yes	09-02-21	02-03-21	Pfizer-BioNtech	16-11-21
15-T	Yes	08-01-21	01-29-21	Pfizer-BioNtech	16-11-21
16-T	Yes	06-23-21	07-15-21	Pfizer-BioNtech	16-11-21
17-T	Yes	05-19-21	06-23-21	Moderna	16-11-21
18-T	Yes	03-12-21	09-06-21	AstraZeneca	16-11-21
19-T	Yes	05-25-21	16-06-21	Pfizer-BioNtech	16-11-21
20-T	Yes	06-13-21	07-18-21	Pfizer-BioNtech	16-11-21
21-T	Yes	06-13-21	07-18-21	Pfizer-BioNtech	16-11-21
22-T	Yes	06-22-21	07-27-21	Pfizer-BioNtech	16-11-21
23-T	Yes	06-30-21	07-29-21	Pfizer-BioNtech	16-11-21
24-T	Yes	07-09-21		Johnson&Johnson	16-11-21
25-T	Yes	05-19-21	06-23-21	Pfizer-BioNtech	16-11-21
26-T	Yes	05-14-21	18-06-21	Pfizer-BioNtech	16-11-21
27-T	Yes	05-05-21	09-06-21	Pfizer-BioNtech	16-11-21
28-T	Yes	05-06-21	10-07-21	Pfizer-BioNtech	16-11-21
29-T	Yes	03-01-21	25-01-21	Pfizer-BioNtech	16-11-21

StudySubjectID	Prevaccinated	FDose1	FDose2	Vaccine	FInclusion
31-T	Yes	09-03-21	05-26-21	AstraZeneca	11-17-21

15.6.6 Previous treatment data

ID	Drug	Reason	Frequency	Unit	Use time	time unit
04-T	Allergies	Hydrocortisone	Occasionally	mg	7	years
04-T	Allergies	Antihistamine	Occasionally	mg	7	years
05-T	Psoriasis	Calcipotriol	Daily	mg	10	years
05-T	Psoriasis	Betamethasone	Daily	mg	10	years
17-T	Bronchial asthma	Beclomethasone	Every 12 hours	mg	3	years
17-T	Bronchial asthma	Montelukast	Daily	mg	3	years
22-T	Allergy	Zyrtech	Occasionally	mg	28	years

15.6.7 Individual Efficacy Response Data

15.6.7.1 IgG Antibody Concentration and Molecular Neutralization Titers

ID	previous vaccination	IGG_T0	IGG_28	Seroconv index.	Seroconv.	mVNT_0	mVNT_28
01-T	Pfizer-BioNtech	315.12	1514.56	4.81	Yes	207	501
02-T	Johnson&Johnson	145.25	827.52	5.7	Yes	117	263
03-T	Pfizer-BioNtech	876.08	5852.16	6.68	Yes	484	3528
04-T	AstraZeneca	202	4813.44	23.83	Yes	268	2765
05-T	Moderna	1589.76	26565.12	16.71	Yes	623	9340
06-T	Pfizer-BioNtech	266	3696.96	13.9	Yes	159	2094
07-T	AstraZeneca	72.46	1756.16	24.24	Yes	12.5	592
08-T	Pfizer-BioNtech	741.2	2409.92	3.25	No	283	1540
09-T	Pfizer-BioNtech	573.28	2201.28	3.84	No	147	1111
10-T	Pfizer-BioNtech	4924.8	21116.16	4.29	Yes	2199	8648
11-T	Pfizer-BioNtech	2043.36	37268.48	18.24	Yes	747	21829
12-T	Pfizer-BioNtech	373.52	2470.4	6.61	Yes	163	1070
13-T	Johnson&Johnson	17.32	776.96	44.86	Yes	two	206
14-T	Pfizer-BioNtech	74.44	19762.68	265.48	Yes	40	12654
15-T	Pfizer-BioNtech	34.35	955.52	27.82	Yes	12.5	1227
16-T	Pfizer-BioNtech	447.92	3190.08	7.12	Yes	163	933
17-T	Moderna	664.56	5687.68	8.56	Yes	536	5087
18-T	AstraZeneca	105.76	1648	15.58	Yes	79	870
19-T	Pfizer-BioNtech	300.64	894.72	2.98	No	118	655
20-T	Pfizer-BioNtech	888.48	7215.04	8.12	Yes	917	5090
21-T	Pfizer-BioNtech	764.8	3974.72	5.2	Yes	331	1736

ID	previous vaccination	IGG_T0	IGG_28	Seroconv index.	Seroconv.	mVNT_0	mVNT_28
22-T	Pfizer-BioNtech	577.52	2133.12	3.69	No	154	582
23-T	Pfizer-BioNtech	787.2	1760.32	2.24	No	299	938
24-T	Johnson&Johnson	38.16	536.96	14.07	Yes	12.5	149
25-T	Pfizer-BioNtech	208.77	1035.84	4.96	Yes	43	793
26-T	Pfizer-BioNtech	555.36	13242.24	23.84	Yes	224	6175
27-T	Pfizer-BioNtech	279.68	4882.88	17.46	Yes	198	4212
28-T	Pfizer-BioNtech	939.44	2985.6	3.18	No	625	1032
29-T	Pfizer-BioNtech	287.26	75514.88	262.88	Yes	115	21402
31-T	AstraZeneca	140.71	3477.76	24.72	Yes	132	5142

15.6.7.2 % Inhibition of RBD:ACE2 interaction

ID	Previous vaccination	Inhibition 0	Inhibition 28
01-T	Pfizer-BioNtech	59.4	92.1
02-T	Johnson&Johnson	48.3	85.9
03-T	Pfizer-BioNtech	86.7	94.1
04-T	AstraZeneca	82.9	89.1
05-T	Moderna	89.8	91.9
06-T	Pfizer-BioNtech	62.3	94.2
07-T	AstraZeneca	20.6	91.6
08-T	Pfizer-BioNtech	79.1	88.0
09-T	Pfizer-BioNtech	57.9	91.0
10-T	Pfizer-BioNtech	93.2	90.6
11-T	Pfizer-BioNtech	91.4	92.3
12-T	Pfizer-BioNtech	60.1	92.0
13-T	Johnson&Johnson	12.9	80.4
14-T	Pfizer-BioNtech	27.6	91.1
15-T	Pfizer-BioNtech	24.2	89.9
16-T	Pfizer-BioNtech	61.2	93.3
17-T	Moderna	94.3	91.9
18-T	AstraZeneca	39.7	90.9
19-T	Pfizer-BioNtech	51.1	90.3
20-T	Pfizer-BioNtech	91.3	93.9
21-T	Pfizer-BioNtech	75.5	91.4
22-T	Pfizer-BioNtech	57.1	94.3
23-T	Pfizer-BioNtech	77.5	89.9
24-T	Johnson&Johnson	9.8	65.5
25-T	Pfizer-BioNtech	22.2	88.0
26-T	Pfizer-BioNtech	84.3	91.6
27-T	Pfizer-BioNtech	62.6	91.8

ID	Previous vaccination	Inhibition 0	Inhibition 28
28-T	Pfizer-BioNtech	91.6	92.7
29-T	Pfizer-BioNtech	49.8	94.1
31-T	AstraZeneca	52.2	92.0

15.6.7.3 Viral neutralization titers obtained at the Cuban Civil Defense Laboratory

ID	Treatment	cVNT 0				cVNT 28			
		D614G	Beta	Delta	Omicron	D614G	Beta	Delta	Omicron
01-T	Pfizer-BioNtech	1:20	1:10	1:10	1:10	1:112	1:14	1:80	1:80
02-T	Johnson&Johnson	1:56	0	1:28	1:14	1:320	1:40	1:56	1:160
03-T	Pfizer-BioNtech	1:112	1:5	1:80	1:40	1:320	1:224	1:891	1:1280
04-T	AstraZeneca	1:28	1:5	1:7	1:7	1:447	1:224	1:891	1:1280
05-T	Moderna	1:56	1:56	1:56	1:56	1:1280	1:891	1:1778	1:891
06-T	Pfizer-BioNtech	1:56	1:20	1:20	1:5	1:224	1:447	1:640	1:640
07-T	AstraZeneca	1:7	0	1:5	1:10	1:447	1:224	1:320	1:320
08-T	Pfizer-BioNtech	1:40	1:10	1:28	1:56	1:320	1:160	1:224	1:891
09-T	Pfizer-BioNtech	1:56	1:5	1:20	1:20	1:224	1:56	1:320	1:160
10-T	Pfizer-BioNtech	1:447	1:80	1:320	1:160	1:1778	1:1280	1:320	1:891
11-T	Pfizer-BioNtech	1:56	1:10	1:40	1:56	1:2560	1:1280	1:1778	1:7778
12-T	Pfizer-BioNtech	1:40	0	1:28	1:40	1:640	1:40	1:1280	1:640
13-T	Johnson&Johnson	1:5	0	0	1:7	1:112	1:14	1:56	1:80
14-T	Pfizer-BioNtech	1:7	0	0	1:10	1:3550	1:891	1:2560	1:20480
15-T	Pfizer-BioNtech	1:10	0	0	1:5	1:320	1:20	1:160	1:160
16-T	Pfizer-BioNtech	1:40	1:14	1:7	1:28	1:320	1:112	1:640	1:1280
17-T	Moderna	1:160	1:10	1:5	1:80	1:1280	1:160	1:891	1:640
18-T	AstraZeneca	1:28	0	1:28	1:20	1:447	1:112	1:447	1:891
19-T	Pfizer-BioNtech	1:40	0	1:20	1:56	1:112	1:80	1:224	1:1280
20-T	Pfizer-BioNtech	1:112	1:10	1:40	1:112	1:640	1:224	1:891	1:640
21-T	Pfizer-BioNtech	1:56	1:5	1:7	1:40	1:320	1:80	1:320	1:224
22-T	Pfizer-BioNtech	1:56	1:5	1:14	1:20	1:1778	1:40	1:80	1:112
23-T	Pfizer-BioNtech	1:40	1:10	1:20	1:28	1:112	1:20	1:320	1:320
24-T	Johnson&Johnson	1:5	0	0	1:7	1:80	1:7	1:20	1:80
25-T	Pfizer-BioNtech	1:10	0	1:5	1:10	1:112	1:14	1:112	1:56
26-T	Pfizer-BioNtech	1:56	1:5	1:20	1:56	1:1280	1:447	1:3550	1:1280
27-T	Pfizer-BioNtech	1:28	0	1:10	1:28	1:160	1:112	1:320	1:80
28-T	Pfizer-BioNtech	1:80	1:20	1:56	1:56	1:160	1:80	1:320	1:447
29-T	Pfizer-BioNtech	1:56	1:10	1:14	1:56	1:7558	1:1778	1:10240	1:81920
31-T	AstraZeneca	1:40	1:5	1:10	1:40	1:640	1:56	1:447	1:1280

cVNT <1:10 was assumed to be 5

15.6.8 Concomitant therapy data

ID	Drug	Treat AE	Frequency	Unit
07-T	CAPTOPRIL	AHT	SINGLE DOSE	mg
14-T	DIPYRONE	General malaise	SINGLE DOSE	mg
27-T	DICLOFENAC	Neck contracture	SINGLE DOSE	mg

15.6.9 Lists of adverse events

ID	Previous vaccination	AE	Appearance	Duration	Intens.	Gravity	Results	Causality
REQUESTED-LOCAL								
01-T	Pfizer-BioNtech	Pain	60-24 hours	>24-48h	Mild	not serious	Resolved	A1
02-T	Johnson&Johnson	Pain	60-24 hours	<=24h	Mild	not serious	Resolved	A1
03-T	Pfizer-BioNtech	Pain	60-24 hours	<=24h	Mild	not serious	Resolved	A1
06-T	Pfizer-BioNtech	Pain	60-24 hours	<=24h	Mild	not serious	Resolved	A1
07-T	AstraZeneca	Pain	60-24 hours	>24-48h	Mild	not serious	Resolved	A1
14-T	Pfizer-BioNtech	Pain	60-24 hours	>48-72h	Mild	not serious	Resolved	A1
15-T	Pfizer-BioNtech	Pain	60-24 hours	>24-48h	Mild	not serious	Resolved	A1
17-T	Moderna	Pain	60-24 hours	>24-48h	Mild	not serious	Resolved	A1
22-T	Pfizer-BioNtech	Pain	60-24 hours	>24-48h	Mild	not serious	Resolved	A1
27-T	Pfizer-BioNtech	Pain	60-24 hours	<=24h	Mild	not serious	Resolved	A1
29-T	Pfizer-BioNtech	Pain	60-24 hours	<=24h	Mild	not serious	Resolved	A1
UNSOLICITED-LOCAL								
07-T	AstraZeneca	Pruritus vaccination site	<=60min	<=24h	Mild	not serious	Resolved	A1
UNSOLICITED-SYSTEMIC								
07-T	AstraZeneca	Arterial hypertension	60-24 hours	<=24h	Mild	not serious	Resolved	A4
14-T	Pfizer-BioNtech	Throat pain	>72h	>48-72h	Mild	not serious	Resolved	C
14-T	Pfizer-BioNtech	General discomfort	>72h	<=24h	Mild	not serious	Resolved	C

ID	Previous vaccination	AE	Appearance	Duration	Intens.	Gravity	Results	Causality
27-T	Pfizer-BioNtech	Muscle contracture in the neck	>48-72h	<=24h	Mild	not serious	Resolved	C

15.6.10 List of laboratory measurements

ID	Rapid Pregnancy Test	Rapid antigen test	PCR
01-T	NA	black	black
02-T	NA	black	black
03-T	Black	black	black
04-T	NA	black	black
05-T	NA	black	black
06-T	NA	black	black
07-T	NA	black	black
08-T	NA	black	black
09-T	Black	black	black
10-T	NA	black	black
11-T	NA	black	black
12-T	Black	black	black
13-T	NA	black	black
14-T	NA	black	black
15-T	NA	black	black
16-T	Black	black	black
17-T	NA	black	black
18-T	NA	black	black
19-T	NA	black	black
20-T	Black	black	black
21-T	NA	black	black
22-T	Black	black	black
23-T	NA	black	black
24-T	NA	black	black
25-T	NA	black	black
26-T	Black	black	black
27-T	NA	black	black
28-T	NA	black	black
29-T	NA	black	black
31-T	NA	black	black

NA: Not applicable. Neg: Negative

15.7 ANNEX 8: RANDOMIZATION SCHEME

The study is open, not randomized. The vaccine was administered in the proposed strength to the subjects included in the study.

15.8 ANNEX 9: AUDIT CERTIFICATES

The reports of the audits carried out by CENCEC are very extensive. We only include the conclusive "Letter to the Researcher" of each one. On the other hand, four initial evaluations were carried out at the Cuban institutions that participated in the clinical study. Three initiation reports, and three completion reports, including the Final Conclusion Report.

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Vladimir Daniel Trujillo Machado

Clinical site: International Health Center "La Pradera"

Visit date: 11-16-21 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

During the visit, the entire vaccination process, records and HC are reviewed.

The HC and CRD will be electronically in the Open Clinic software. The main difficulty found is that the data entry in the electronic HC was not started.

Action: The investigators will complete all the data in the HCs.

Responsible: Responsible Investigator and Co-investigators.

Deadline: 10-19-2021

The Contracts between the Promoter with the Site and the different Laboratories are not available.

Action: Ask the sponsor to put the contract in the researcher's folder.

Deadline: 25-11-21

Name and position of the person carrying out the visit: Anaelys R. Maceo Sinabele/ Leani Martínez García. AIC

Signature of the Principal/Responsible Investigator:

LETTER TO INVESTIGATOR

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

EC abbreviated title: Soberana Plus Turin

Name of the Researcher: Gerardo Baró Román

Clinical Site: Immunoassay Center

Visit date: 10/10/21 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

The Delivery Record of the 30 time zero samples and the Delivery Record of the results that were delivered to the IFV cannot be found.

Action: The Responsible Investigator will request a copy of the delivery certificate from Dr.C. Yanet Climent Ruiz**,** responsible for Sample Management.

Deadline: 12-27-21

The researchers maintain a good attitude towards the study and mastery of the protocol.

Name and position of the person making the visit: Anaelys R. Maceo Sinabele. AIC

Signature of the Principal/Responsible Investigator: Gerardo Baró Román

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Tays Hernández García

Clinical Site: Immunology Laboratory Molecular Immunology Center

Visit date: 12/10/21 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

It remains to be signed Models of Delegation of Functions and Duties and Responsibilities Laboratory Co-Investigator.

Deadline: 12-27-21

Name and position of the person carrying out the visit: Anaelys R. Maceo Sinabele, Leani Martínez García. AIC

Signature of the Principal/Responsible Investigator: Dr. Tays Hernández García

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Tays Hernández García

Clinical Site: Immunology Laboratory Molecular Immunology Center

Visit date: 12/27/21 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

The samples corresponding to t28 have not yet arrived from Italy for processing in said Laboratory.

The Co-investigator Dr. Belinda Sánchez Ramírez has yet to sign a model Confidentiality Agreement, Participation Commitment, Delegation of Functions and Duties and Responsibilities Co-Investigator of the Laboratory.

Action: The IR will be in charge of collecting the missing signature.

Deadline: January 2022

Name and position of the person carrying out the visit: Anaelys R. Maceo Sinabele, Leani Martínez García. AIC

Signature of the Principal/Responsible Investigator: Dr. Tays Hernández García

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Name of the Researcher: Gerardo Baró Román

Clinical Site: Immunoassay Center

Visit date: 12/27/21 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

The researchers maintain a good attitude towards the study and mastery of the protocol.

The samples corresponding to t28 have not yet arrived from Italy for processing in said Laboratory.

Name and position of the person making the visit: Anaelys R. Maceo Sinabele. AIC

Signature of the Principal/Responsible Investigator: Gerardo Baró Román

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Vladimir Daniel Trujillo Machado

Clinical site: International Health Center "La Pradera"

Visit date: 01-21-22 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

Time zero and time 28 results of Neutralizing Antibody Titers processed in Italy are missing.

Action: Request results from Investigator in Italy.

Deadline: 07-02-2022

Name and title of the person making the visit: Anaelys R. Maceo Sinabele/Leani Martinez Garcia

Signature of the Principal/Responsible Investigator:

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Tays Hernández García

Clinical Site: Immunology Laboratory Molecular Immunology Center

Visit date: 01/28/22 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

The Co-investigator Dr. Belinda Sánchez Ramírez has yet to sign a model Confidentiality Agreement, Participation Commitment, Delegation of Functions and Duties and Responsibilities Co-Investigator of the Laboratory.

Action: The IR will be in charge of collecting the missing signature.

Deadline: 08-02-22

It is reported that the next visit will be on February 8, it will be the **Completion Visit** since the trial ended.

Name and position of the person carrying out the visit: Anaelys R. Maceo Sinabele, Leani Martínez García. AIC

Signature of the Principal/Responsible Investigator: Dr. Tays Hernández García

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Name of the Researcher: Gerardo Baró Román

Clinical Site: Immunoassay Center

Visit date: 01-28-22 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

The researchers maintain a good attitude towards the study and mastery of the protocol.

It is reported that the next visit will be on February 8, it will be the **Completion Visit** since the trial ended.

Name and position of the person making the visit: Anaelys R. Maceo Sinabele. AIC

Signature of the Principal/Responsible Investigator: Gerardo Baró Román

QUALITY CONTROL VISIT		
Model	Code: –	Version: 9

LETTER TO INVESTIGATOR

EC abbreviated title: Soberana Plus Turin

Researcher Name: Dr. Vladimir Daniel Trujillo Machado

Clinical site: International Health Center "La Pradera"

Visit date: 07-02-22 (dd/mm/yy)

Describe the main deficiencies detected and the agreements reached during the visit for their solution:

Time zero and time 28 results of Neutralizing Antibody Titers processed in Italy are missing.

Action: Request results from Investigator in Italy.

Deadline: 07-03-2022

Name and title of the person making the visit: Anaelys R. Maceo Sinabele/Leani Martinez Garcia

Signature of the Principal/Responsible Investigator:

15.9 ANNEX 10. REPORTING OF SERIOUS ADVERSE EVENTS

No serious adverse events were reported during the study.