

Efficacy and Safety of SOBERANA 02, a COVID-19 conjugate vaccine in heterologous three doses combination.

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Abstract (word count 289) , main (word count 2440) 1Table, 4 Figures.

ABSTRACT

Background: SOBERANA 02 is a COVID19 conjugate vaccine (recombinant RBD conjugated to tetanus toxoid). Phase 1 and 2 clinical trials demonstrated its high immunogenicity, promoting neutralizing IgG together with specific T-cell response. A third dose of SOBERANA Plus (SARS-CoV-2 RBD-dimer) further increased the specific anti-RBD neutralizing antibodies.

Methods: In a randomized, double-blinded, placebo-controlled, phase 3 trial we randomly assigned 44 031 participants, aged 19-80 years to three groups in a 1:1:1 ratio to receive 28 days apart either a) two doses of 25 µg SOBERANA 02, or b) two doses of 25 µg SOBERANA 02 followed by a third dose of 50 µg SOBERANA Plus, or c) two doses of placebo. Reported study endpoints are vaccine efficacy (VE) evaluated through laboratory-confirmed symptomatic COVID-19 cases and safety. During the trial, the SARS CoV-2 isolates in Havana were predominantly (β, 74.0 %) and shift gradually to δ (100%).

Results: Two doses of SOBERANA 02 protects against symptomatic COVID-19: 43 cases in the two-dose group (14 371) vs. 155 in the placebo group (14 403), VE 71.0%, adjusted (CI 95%58.9-79.1). The heterologous three dose combination with SOBERANA Plus protected against symptomatic COVID-19: 15 cases in the vaccine groups (13 833) vs. 155 in the placebo group (14 303), VE 92.4%, adjusted (CI 95% 86.9-95.6%). For two-dose schedule VE against severe COVID-19 was 63.0% and for death 59.0%; for heterologous three-dose schedule, 100% in both cases.

Conclusions: This is the first phase 3 study of a three-dose, heterologous vaccine combination against SARS-CoV-2. Two doses of the conjugate vaccine SOBERANA 02 was safe and attained efficacy of 71.0% in adult's population 19-80 y/o; incorporating SOBERANA Plus after two doses of SOBERANA 02, increased efficacy from 71.0 % to 92.4% (Clinical Trials IFV/COR/09 number, RPCEC00000354.)

Introduction

Vaccination represents the main tool in the fight against COVID-19 pandemic. The speed of vaccination is critical to control the emergency and spreading of new virus variants. [1] SOBERANA 02 is the first conjugated vaccine developed for SARS CoV-2. The antigen is the recombinant receptor binding domain (RBD) protein conjugated chemically to tetanus toxoid (TT) in a molar ratio 6/1.[2] The development of protein-polysaccharide conjugation technology in the 1980s furnished safe, highly immunogenic novel pediatric vaccines against *Haemophilus influenzae* type b [3]. Other conjugate vaccines based on carbohydrate antigens are in use in pediatric population for *Neisseria meningitidis* and *Streptococcus pneumoniae* [4, 5, 6, 7]. None is for SARS CoV-2 prevention.

A single dose of SOBERANA Plus is an excellent booster of natural immunity in convalescent [8] through a mechanism named hybrid immunity [9]. In a phase 1 and 2a clinical trials, two doses of SOBERANA 02 induced neutralizing antibodies and B and T-cell memory with a typical IFN γ secretion, Th1 pattern.[10] SOBERANA Plus-as third dose- significantly increased neutralizing anti-RBD IgG. These results were confirmed in a phase 2b clinical trial, paving the way to launch the phase 3 trial.

This phase 3 trial (IFV/COR/09 number, RPCEC00000354) evaluates the safety and efficacy of two immunization regimes: a) two doses of SOBERANA 02 and b) its heterologous combination with SOBERANA Plus as the third dose. These are the results of the final analyses.

Methods

Study Design, Oversight and Ethics

A double-blind, randomized, placebo-controlled, stratified, case-driven phase 3 clinical trial recruited adult participants in medically stable condition from 48 sites in eight Havana municipalities. Participants recruited from March 8 to March 31, 2021 by community family doctors provided written informed consent. The trial adheres to the principles of the Helsinki's Declaration and to the Good Clinical Practice guidelines of the International Council for Harmonization. The Central Research Ethics Committee from the Cuban Ministry of Health was *ad hoc* appointed for this trial. They approved the protocol (Clinical Trials IFV/COR/09 number, RPCEC00000354) and the consent forms. (Details on

procedures are provided in the protocol and Supplementary Information (SI) available upon publication).

The Cuban National Center for the Coordination of Clinical Trials (CENCEC) monitored the trial in terms of adherence to the protocol and Good Clinical Practice as well as data accuracy. An unblinded independent data and safety monitoring board (IDSMB) continuously monitored safety and conducted interim analysis (IA). The trial was designed, conducted and sponsored by The Finlay Vaccine Institute. Data analysis and interpretation were performed by the research team. The SOBERANA 02 team collected data and contributed to their interpretation.

Participants, randomization and data blinding

Volunteers aged 19–80 years were screened for eligibility at clinical sites. A full list of exclusion criteria is provided with the study protocol available upon publication. Three groups were conformed to receive; two doses of SOBERANA 02 (group A); two doses of SOBERANA 02 followed by a third dose of SOBERANA Plus (heterologous scheme group B); and placebo (two doses) administered 28 days apart. Randomization into study arms (A and B) and placebo was done on day 0 at a 1:1:1 ratio using a site stratified random and previously defined risk strata (19-64 years without risk comorbidities, 19-64 years with risk comorbidities and ≥ 65 years). Participants at risk of severe COVID-19 disease were defined in the protocol available upon publication. In the event of a medical emergency requiring acute intervention, the masking was planned to be remove, upon the approval of the responsible investigator and the IDSMB's knowledge.

Trial vaccines/placebo

SOBERANA 02 antigen is the recombinant RBD from SARS-CoV-2 (25 μg) chemically conjugated to TT in a molar ratio $\sim 6/1$ and adsorbed on 500 μg alumina [2]. SOBERANA Plus was develop as a universal booster; the antigen is dimeric RBD (50 μg) adsorbed on 1250 μg alumina [11]. The placebo contained all ingredients except the active principle. Vaccine and placebo were indistinguishable to ensure product masking. Both were stored at 2° to 8°C and distributed daily to the clinical site by a logistic specialized operator.

Safety

AEs were classified as solicited and unsolicited; as mild, moderate and severe; and vaccine related or non-related. Frequencies were calculated after each vaccine/placebo dose: solicited local and systemic, during 7 days; unsolicited, during 28 days; leading to protocol discontinuation, demanding medical attention or classified as serious, during 30 days. IDSMB continuously monitored cases of COVID-19 and severe COVID-19. Safety was evaluated in the “Safety Population”(SP): participants receiving at least one dose of the vaccine candidates or placebo.

Efficacy

The primary endpoint was VE in preventing the occurrence of symptomatic COVID-19 confirmed by positive SARS-CoV-2 RT-PCR nasopharyngeal swab (RT-PCR) with onset at least 14 days after the last injection in the per-protocol population (PPP). Primary endpoint was judged blinded by COVID-19 hospital doctors, reviewed by specially trained doctors and finally by the study’s Principal Investigator (PI).

COVID-19 symptomatic disease was considered if participants had at least one major symptom or sign or two minor symptoms (major signs or symptoms: dyspnea, oxygen saturation $\leq 92\%$, persistent thoracic pain, neurological disorders, clinical or radiographic evidence of pneumonia; minor symptoms: fever, chills, myalgia, headache, sore throat, running nose, diarrhea/vomits, myalgia, malaise, cough, dysgeusia/anosmia). RT-PCR was conducted by the SARS CoV-2 National reference laboratory at the “Pedro Kouri” Tropical Medical Institute, Havana, Cuba. Participants with symptoms or reporting direct contact with a positive RT-PCR person were allocated to a COVID-19 hospital designed by the Ministry of Health and showed their “study’s identity card”. After a positive RT-PCR, they were hospitalized and daily followed to assess symptom severity, until hospital discharge after negative RT-PCR and symptoms resolved.

VE at the primary endpoint was evaluated across risk strata for severe disease (19-64 years without risk comorbidities; 19-64 years with risk comorbidities; and ≥ 65 years), sex (female or male), and skin color (white, black and mixed-race). Secondary outcomes for VE were severe systemic confirmed COVID-19 disease (serious or critical), defined by one of the following criteria: polypnea; x-rays infiltration/condensation, pulmonary echography; oxygen saturation $\leq 90\%$ or assisted mechanic ventilation (serious disease),

acute respiratory distress syndrome or evidence of septic shock (critical disease). (Other secondary outcomes are included in SI upon publication).

Statistical analysis

To evaluate the primary VE end point, the trial was designed with the hypothesis that the risk of symptomatic disease is reduced more than 60% compared to placebo group. The lower limit of the 95% confidence interval (CI) was $\geq 30\%$, which points to the rejection of the null hypothesis (that the efficacy of either vaccination scheme is $\leq 30\%$)[12]. VE was calculated as the percentage reduction in the hazard ratio (HR) as $VE = 100 \times (1 - HR) \%$, in the vaccine groups as compared with placebo, separately, with HR estimated from a stratified Cox proportional hazards model. The design required to achieve 90% power (and 2.5% 1-sided type I error) to detect a HR of 0.4 (VE >60% to reduce the risk of symptomatic disease compared to placebo), with a null hypothesis HR of 0.7. VE bounds were derived using a Lan-DeMets O'Brien-Fleming approximation spending function. Two interim analyses (IA) were planned to be performed when detecting 53 and 106 symptomatic cases meeting the primary outcome definition more than 14 days after the last dose of the corresponding schedule.

A stopping criterion due to unacceptable toxicity (when the frequency surpassed 1%) was evaluated iteratively, with a Bayesian algorithm (SI upon publication).

Results

Trial Population

Recruited participants (44 031) underwent randomization (mean age: 48 years, 52 % female, 18% ≥ 65 years, 28% 19-64 years with comorbidities) as follows: group A: 14 679 (two doses, SOBERANA 02), group B: 14 677 (three doses heterologous schedule) and group C: 14 675 (placebo) (Fig. 1). Baseline demographic characteristics were balanced

between the placebo group and the intervention groups (Table 1). Demographic characteristics were balanced between the placebo group and the intervention groups (Table 1). The racial or ethnic proportions of represented Cuban demographics. Evidence of previous SARS-CoV-2 infection at baseline as detected by serologic rapid test testing was present in 0.4% participants.

173 participants withdraw their consent and didn't receive the 2nd dose and 286 didn't receive the 3rd dose. Participants were excluded when detected positive RT-PCR before the administration of the 2nd dose (407 participants) and before the 3th dose (123 participants). Primary efficacy and safety were analyzed in PPP and SP respectively. The primary VE analysis included 42 557 participants receiving the first injection: placebo group (14 303), group A (14 371) and group B (13 883); 1 474 participants were excluded from the PPP (Fig. 1): placebo group (372), group A (308) and group B (794). The participants had a median follow-up duration of 50 days (range, 0-156) and 121 days (range, 0-136) after the third dose.

Safety

Solicited AEs at the injection site occurred more frequently in the vaccine group than in the placebo group after both the first dose (7.7%, vs. 2.6%) and the second dose (1.9%, vs. 0.44%) (Fig. 2). After the third dose, the frequency of subjects with injection site AEs was 0.3%. In the vaccine groups A + B, injection site events were predominantly grade 1 in severity and lasted a median of 1 day after the first and second dose, and 2 days after the third dose. The most common injection site AE was pain after injection (2.6% vs. 8.2% in placebo and vaccine, respectively at any time). Delayed injection site reactions (those with onset on or after day 8) were noted in 21 participants (0.05%) after the first dose, 5 (0.01%) after the second dose and 1 after the third dose (0.01%). Reactions were characterized by erythema, induration, and warmth, swelling and pain and all resolved over the following 15 days.

Solicited systemic AEs occurred more often in the vaccine groups than in the placebo group after both the first dose (2.0%, vs. 1.6%), the second dose (0.8%, vs. 0.2%) and 0.1% after the third dose. Their severity in the vaccine groups changed slightly; for grade 2 events, from 6.5% after the first dose to 8.8% after the second dose; for grade 3, from 0.6% to

0.4%. Solicited systemic AEs in the vaccine groups lasted a median of 1 day after the first and second dose, and 2 days after the third dose.

Both solicited injection-site (7.1% vs. 5.1%) and systemic AEs (2.4% vs. 2.2%) were more common among younger participants (19-64 years) than in ≥ 65 years group. AEs frequency reported during the 28 days after injection was similar in all groups: grade 3 AEs in the placebo group (3.8%), in the vaccine groups (3.4% and 4.2%, for groups A and B, respectively) and serious adverse events (7.9%, 6.7% and 6.7% in placebo, A and B groups respectively).

All-cause mortality was unbalanced, 9 and 11 (0.1% each one) among vaccine recipients and 24 (0.2%) in placebo recipients.

Efficacy

The final analysis of the two-dose schedule detected 198 cases of COVID-19: 43 in the vaccine group A (0.8 per 1000 person-years; 95% CI, 0.6 to 1.1) and 155 in the placebo group (2.7 per 1000 person-years; 95% CI, 2.3 to 3.2), indicating 71.0% VE (95% CI, 58.9-79.1%; $P < 0.001$) for the prevention of symptomatic SARS-CoV-2 infection as compared to placebo (Fig. 4A).

The final analysis of the three-dose schedule informed 170 cases of Covid-19: 15 cases in the vaccine group B, (0.1 per 1000 person-years; 95% CI, 0.1 to 0.1) and 155 cases in the placebo group, indicating 92.4% VE (95% CI, 86.9-95.6%; $P < 0.001$) for the prevention of symptomatic SARS-CoV-2 infection as compared to placebo (Fig. 4B).

VE against severe COVID-19 was for two-dose schedule 63.0% (2/14731 cases in group A vs 6/14303 cases in placebo), and for heterologous three-dose schedule, 100%. (0/13 883 cases in group B vs 6/14303 cases in placebo). VE for the prevention of COVID-19 death was for two-dose 59.0% (3/14731 cases in group A vs 8/14303 cases in placebo) and for heterologous three-dose schedule 100%. (0/13 883 cases in group B vs 8/14303 cases in placebo).

Discussion

SOBERANA 02 conjugate vaccine is a safe and efficacious vaccine for the prevention of symptomatic COVID-19 in adults' population 19-80 years. The trial was planned for measuring $>60\%$ expected efficacy by protocol when original SARS CoV-2 strain was

predominant in Havana, the trial site. In fact, Two-dose VE of 62% was attained in the IA while the trial was running during predominant transmission of β VOC (74% isolates in Havana) carrying the E484K mutation that substantially reduces its neutralization by antibodies in sera of convalescent and vaccinated persons [13]. At the final analysis a shift from β VOC to δ VOC was already installed in Havana.[14] A higher two-dose VE of 71% was obtained at preventing symptomatic disease. The heterologous third dose of SOBERANA Plus showed however at 91.2% VE at IA and slightly increased to 92.4% at the present final analysis. Noteworthy, VE was invariably high independently of VOC circulating.

A very favorable safety profile was revealed within a median safety follow-up of ~2 months after full vaccination. It was characterized by mild, transient, local reactogenicity and the absence of serious vaccine-related AEs. Unlike other vaccines, systemic AEs were not predominant. Noteworthy, the number of local AEs reported were substantially reduced for the third dose (SOBERANA Plus). This vaccine was previously evaluated in SARS CoV-2 convalescent. [8] The remarkable safety and the increase of efficacy attained here confirm its potential as universal booster; it was highly efficient in preventing severe disease and death, attaining 100 %.

In this study, final VE was computed 14 days after the last immunization; this is, for participants receiving the three-dose heterologous schedule, on day 70 after the first immunization. The main limitation of this study— as of most phase 3, COVID19 VE studies— is the narrow time window for VE evaluation. The waning of immunity over time and its impact on efficacy are key aspects that deserve the highest attention. At present, we are following time evolution of protection as well as its behavior towards new circulating variants; these aspects will be addressed in other communications.

In conclusion, the conjugate vaccine SOBERANA 02 was efficacious and induced cross-protection during a dominant circulation of the VOC β and VOC δ . The third heterologous dose of SOBERANA Plus increase efficacy up to an outstanding 92.4 % preventing severe disease and death.

Taken together, our findings indicate that SOBERANA 02 is a promising vaccine that can be used in a two-dose regime or in heterologous three dose combination with SOBERANA

plus to fight COVID19 pandemic in adults population. According to the safety profile and efficacy, it is a potential vaccine for pediatric age.

[Disclosures]

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Disclosure forms provided by the authors are available with the full text of this article upon publication.

A data sharing statement provided by the authors is available with the full text of this article upon publication

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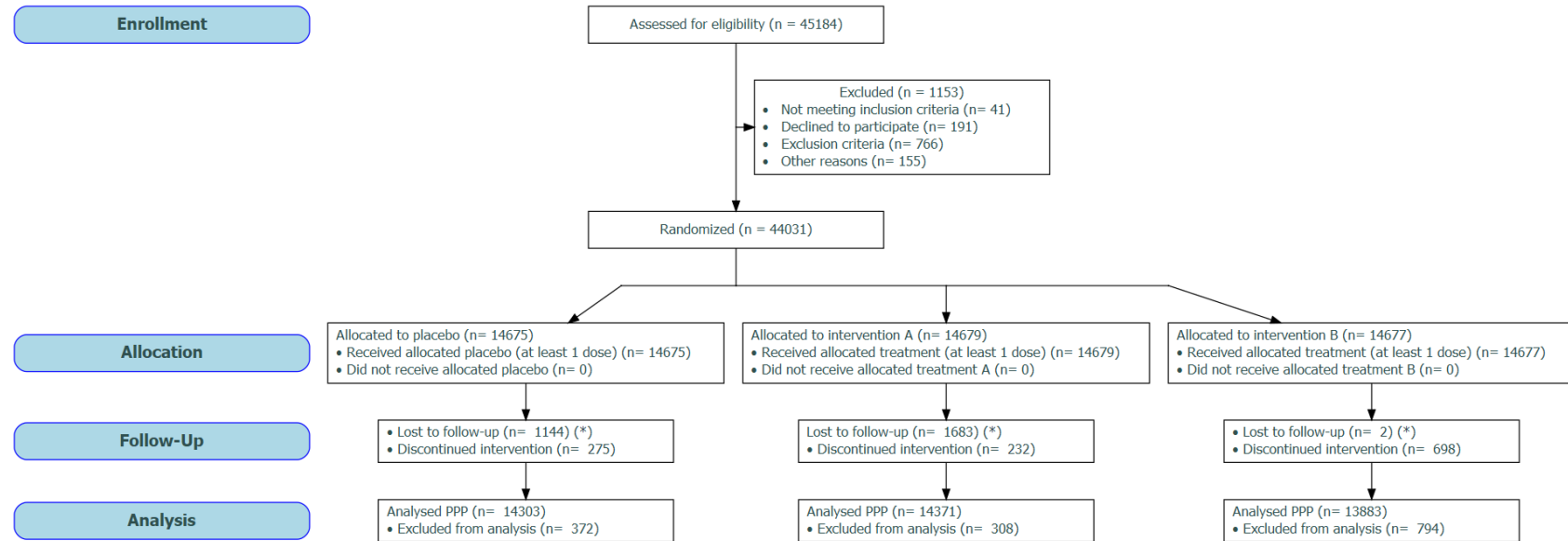
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Figure 1 flowchart§



§Exclusion criteria included: acute infection disease on previous 7 days, mental disorders, known history of COVID-19, history of hypersensitivity to components of the formulations, tetanus toxoid vaccine in the last 3 months, previous SARS-CoV-2 vaccine, any immunomodulatory therapy in the last 30 days, pregnancy, puerperium or breastfeeding, uncontrolled chronic diseases, HIV, unstabilized malignant disease or persons receiving cytostatics and/or radiotherapy.

*"Lost of follow-up" and "discontinued intervention" are not excluded from the analysis

Table 1. Demographics and clinical characteristics at baseline.

Characteristic	Treatment Received§			
	Overall N = 44,031 ¹	Placebo N = 14,675 ¹	Group A N = 14,679 ¹	Group B N = 14,677 ¹
Age - Mean (range) - years	48 (18-81)	48 (18-81)	48 (18-81)	49 (18-81)
Race or ethnic group - n (%)				
Black	7,276 (17%)	2,453 (17%)	2,379 (16%)	2,444 (17%)
Mixed-race	10,738 (24%)	3,574 (24%)	3,575 (24%)	3,589 (24%)
White	26,017 (59%)	8,648 (59%)	8,725 (59%)	8,644 (59%)
Sex - n(%)				
F	23,102 (52%)	7,662 (52%)	7,694 (52%)	7,746 (53%)
M	20,929 (48%)	7,013 (48%)	6,985 (48%)	6,931 (47%)
Comorbidities - n (%)*	18,074 (41%)	5,968 (41%)	6,064 (41%)	6,042 (41%)
Asthma - n(%)	2,926 (6.6%)	994 (6.8%)	945 (6.4%)	987 (6.7%)
COPD - n (%)	311 (0.7%)	95 (0.6%)	104 (0.7%)	112 (0.8%)
Cancer - n (%)	263 (0.6%)	96 (0.7%)	79 (0.5%)	88 (0.6%)
Obesity - n(%)	1,772 (4.0%)	592 (4.0%)	577 (3.9%)	603 (4.1%)
Cardiovascular disease n(%)	1,336 (3.0%)	454 (3.1%)	430 (2.9%)	452 (3.1%)
Diabetes mellitus n(%)	3,673 (8.3%)	1,194 (8.1%)	1,224 (8.3%)	1,255 (8.6%)
CKD n(%)	111 (0.3%)	40 (0.3%)	36 (0.2%)	35 (0.2%)
Immunodeficiency - n(%)	2,636 (6.0%)	870 (5.9%)	872 (5.9%)	894 (6.1%)
HBP- n (%)	13,703 (31%)	4,529 (31%)	4,572 (31%)	4,602 (31%)
Severe malnutrition n(%)	354 (0.8%)	120 (0.8%)	128 (0.9%)	106 (0.7%)
Age category and risk for severe Covid-19 (strata) - n (%)				
≥65 years	7,908 (18%)	2,634 (18%)	2,639 (18%)	2,635 (18%)
19-64 years	23,642 (54%)	7,895 (54%)	7,875 (54%)	7,872 (54%)
19-64 years with comorbidities	12,481 (28%)	4,146 (28%)	4,165 (28%)	4,170 (28%)
Baseline RT-PCR test - n (%)				
Negative	44,009 (100%)	14,666 (100%)	14,676 (100%)	14,667 (100%)
Positive	22 (<0.1%)	9 (<0.1%)	3 (<0.1%)	10 (<0.1%)
Baseline IgM anti-SARS-CoV-2 rapid test - n (%)				
Negative	44,013 (100%)	14,670 (100%)	14,673 (100%)	14,670 (100%)
Positive	18 (<0.1%)	5 (<0.1%)	6 (<0.1%)	7 (<0.1%)
Baseline IgG anti-SARS-CoV-2 rapid test - n (%)				
Negative	43,947 (100%)	14,644 (100%)	14,651 (100%)	14,652 (100%)
Positive	84 (0.2%)	31 (0.2%)	28 (0.2%)	25 (0.2%)

¹Mean (Range) or Frequency (%)

§Treatment received:

Placebo;

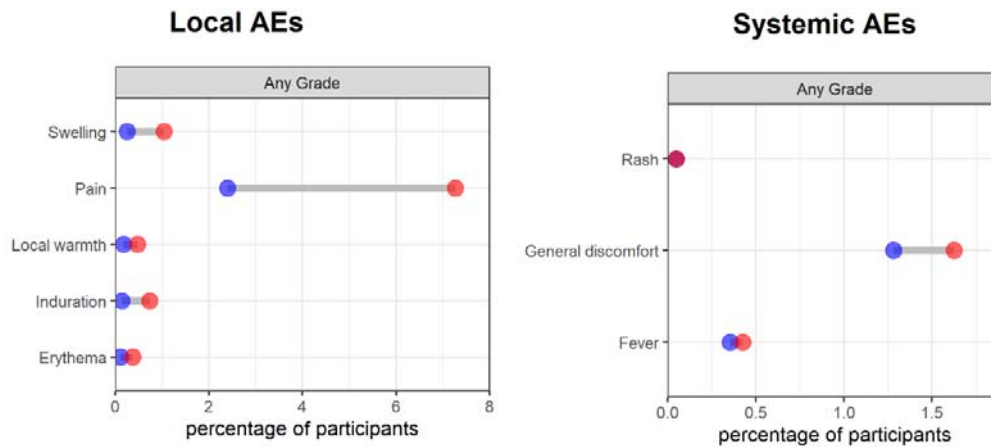
Group A- Two doses of SOBERANA 02, 28 days apart;

Group B- Two doses of SOBERANA 02 and 1 dose of SOBERANA PLUS, 28 days apart.

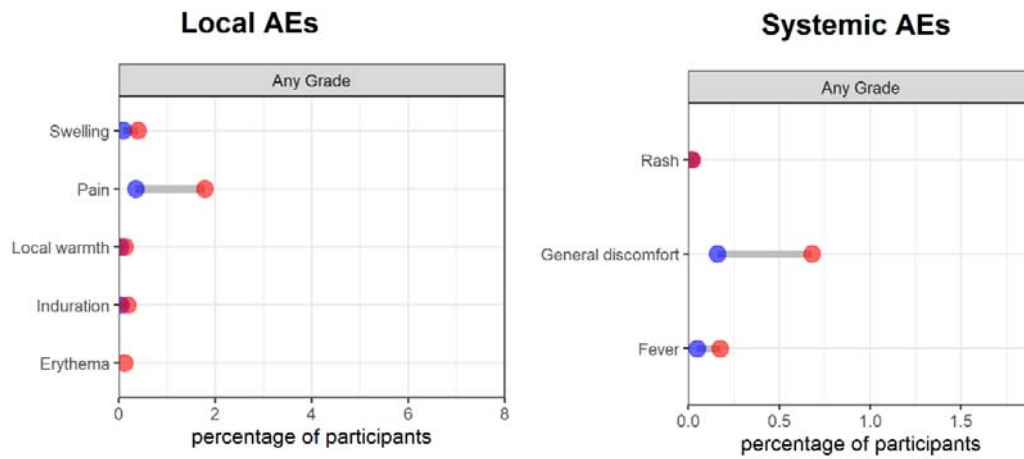
*Participants with risk's comorbidities of severe COVID-19 disease were considered with at least one of these conditions: moderate-to-severe asthma; chronic obstructive pulmonary disease (COPD); cancer; severe obesity (body mass index [the weight in kilograms divided by the square of the height in meters] ≥40), cardiovascular disease; diabetes (type 1 or type 2); chronic kidney disease (CKD); controlled or uncontrolled high blood pressure (HBP), other immunodeficiency and severe malnutrition.

Figure 2. Comparative plot of Solicited Local and Systemic Adverse Events.*

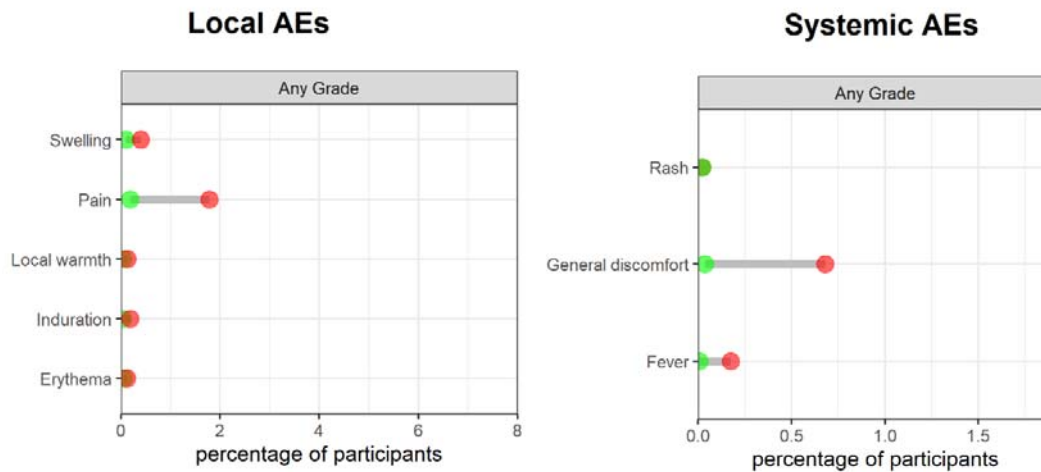
1 dose SOBERANA 02 vs Placebo



2 dose SOBERANA 02 vs Placebo

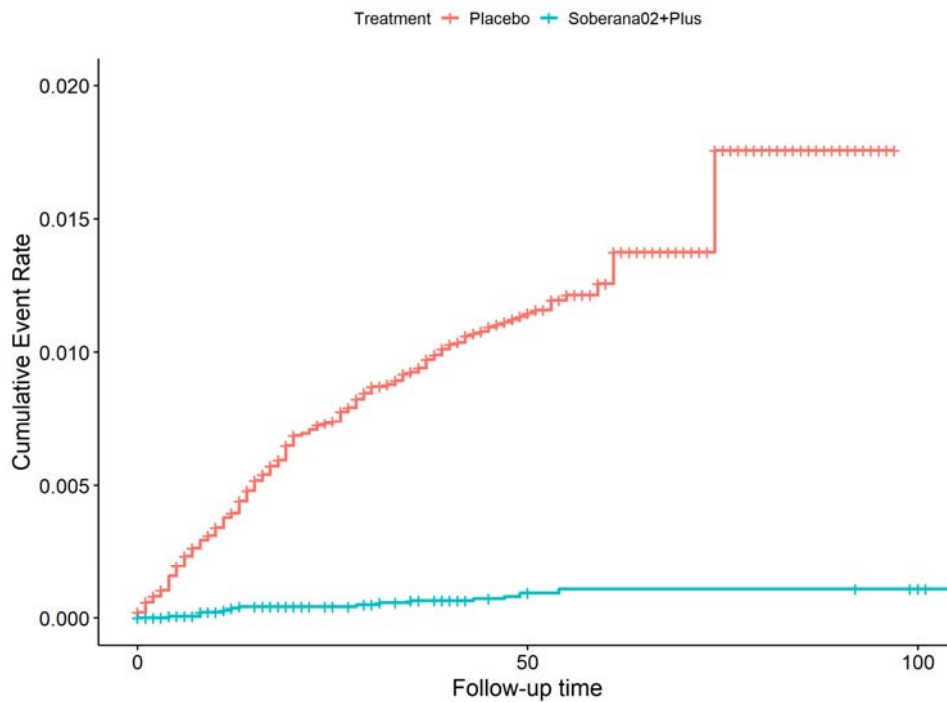
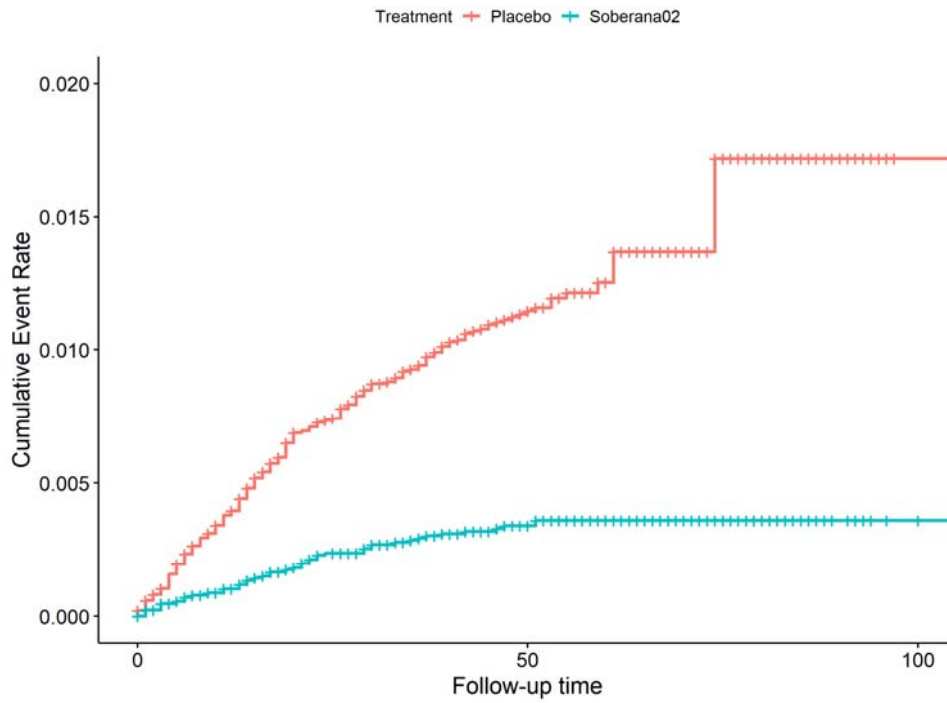


3 dose SOBERANA Plus vs SOBERANA 02



* Comparative plot: The percentage of participants with solicited local and systemic AEs during the 7 days after each vaccination (any grade: mild, moderate, severe).

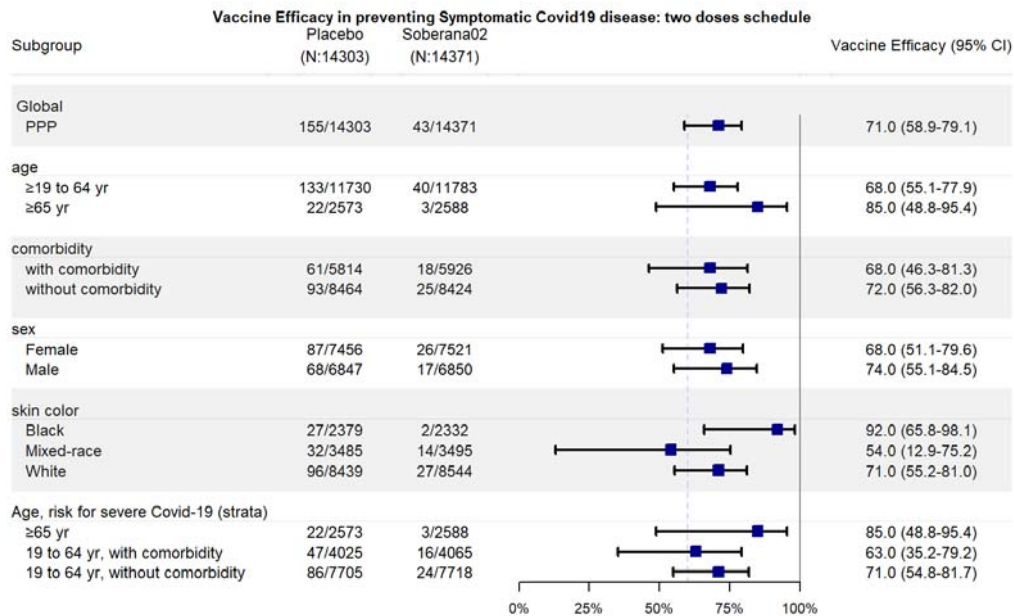
Figure 3. Cumulative incidence plots of symptomatic Covid-19 for two-dose schedule (SOBERANA 02) or heterologous three dose schedule (SOBERANA 02 + SOBERANA Plus).



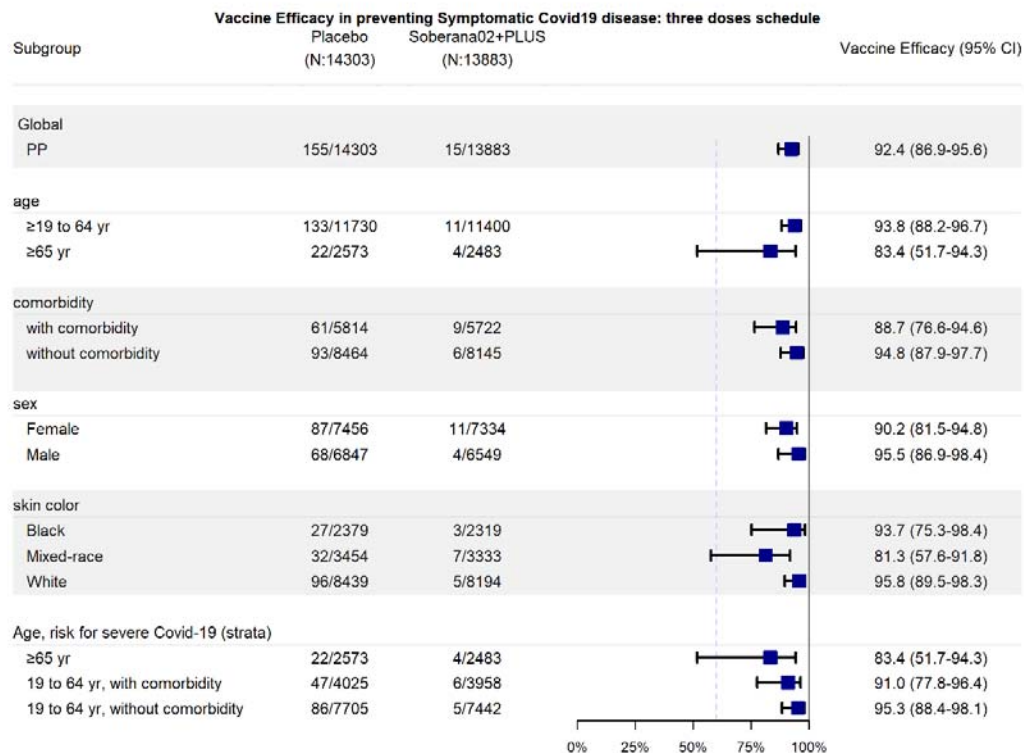
The time period for surveillance of the full analysis population was from 14 days after receipt of the last vaccine dose through approximately ~2 months of follow-up

Figure 4. VE of SOBERANA 02 in Specific Subgroups in the Per-Protocol Population.

A) VE of two doses schedule (SOBERANA 02)



B) VE of three doses schedule (SOBERANA 02 + SOBERANA Plus)



VE was defined as 1 minus the relative risk (full regime (A or B) vs. placebo).