**Title: Immunogenicity evaluation of the heterologous combination of two doses of SINOPHARM and one dose of SOBERANA Plus: a post-authorization study for emergency use.**

Como parte de una intervención sanitaria realizada por el Ministerio de Salud Pública, en la provincia de Cienfuegos se administró un esquema de vacunación heterólogo de una dosis de SOBERANA® Plus posterior a las dos dosis de la vacuna BBIBP-CorV (0-21-42) a toda la población mayor de 19 años; se aplicaron 269.755 dosis de vacuna inactivada y 129.588 dosis de SOBERANA® Plus.

During a sanitary intervention done by the Ministry of Public Health in Cienfuegos province, an heterologous immunization schedule of a dose of SOBERANA® Plus was administered after the two doses of BBIBP-CorV vaccine (0-21-42) to the entire population over 19 years of age; 269,755 doses of the inactivated vaccine and 129,588 doses of SOBERANA® Plus were applied. At the moment of this intervention, SINOPHARM vaccine was prequalified by WHO and SOBERANA Plus had Emergency Use Authorization granted by the CECMED.

Of the total number of vaccinated people, a cohort was selected in the municipalities of Palmira and Cruces that included 202 subjects over 19 years of age who gave their consent to participate in the evaluation of the immunogenicity of the application of the heterologous scheme, of which 131 subjects were between 19 and 59 years old and 71 subjects older than 60 years.

The results obtained in the concentration of specific anti-RBD antibodies after applying two doses of BBIBP-CorV and 21 days after receiving the booster dose of SOBERANA® Plus, increase the level of specific anti-RBD antibodies after the third dose.

In subjects vaccinated with two doses of BBIBP-CorV, a median anti-RBD IgG concentration of 18.5 AU/mL is achieved. When applying the third dose, the concentration value increases more than 8 times, reaching a median of 146.6 AU/mL. Statistically significant differences were detected when applying SOBERANA® Plus.

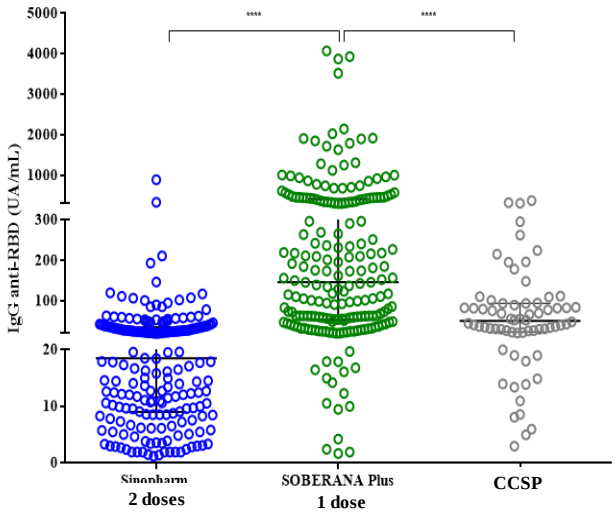


***Figure 1.*** *Anti-RBD IgG antibodies induced by two doses of BBIBP-CorV (blue) and by a dose of SOBERANA® Plus(green) expressed in arbitrary units/mL. The median (25-75 percentile) is represented. The * represent significant differences, as indicated. CCSP: Cuban Convalescent Serum Panel.*

According to age groups, divided into subjects from 19 to 59 years and older than 60 years; when analyzing the immune response in subjects aged 19 to 59 years, a significant increase in the concentration levels of antibodies induced by applying the booster dose was evidenced with an increase of approximately 8 and 7.7 times with respect to the median after 2 doses of Sinopharm, in subjects between 19-59 years and those greater than or equal to 60 years, respectively. This value was also significant when compared to the median of the panel of Cuban convalescents, with an increase of 3.3 times. In the case of subjects over 60 years of age, values similar to those of the younger population were obtained, with a median antibody concentration after two doses of 15 AU/mL that increased 7 times after the booster dose, reaching a median of 106.3 AU/mL, which represents an increase of 2.1 times the values of the convalescent panel.

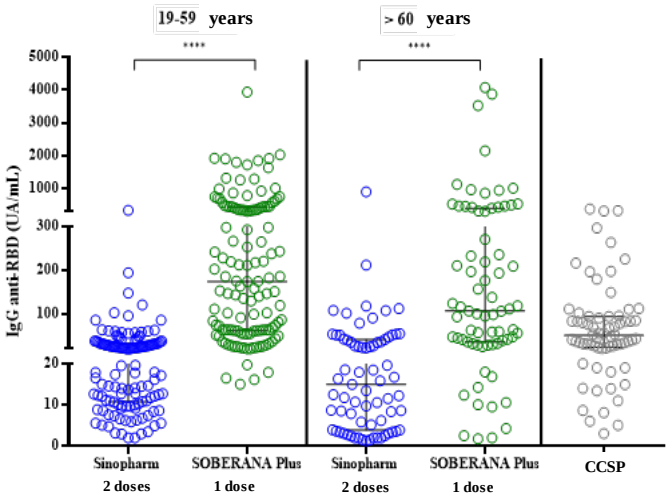


***Figure 2.*** *Anti-RBD IgG antibodies induced by two doses of BBIBP-CorV (blue) and by a dose of SOBERANA® Plus(green) by age group, expressed in arbitrary units/mL. The median (25-75 percentile) is represented. The * represent significant differences, as indicated. CCSP: Cuban Convalescent Serum Panel.*

The inhibition ratio of RBD-ACE2 interaction is a measure of the quality of the antibodies induced by vaccination. When evaluating the capacity of the antibodies to inhibit the RBD: ACE2 interaction after two doses, a median of 30.8% is observed, while when they receive the third dose, this value reaches 86.6%.

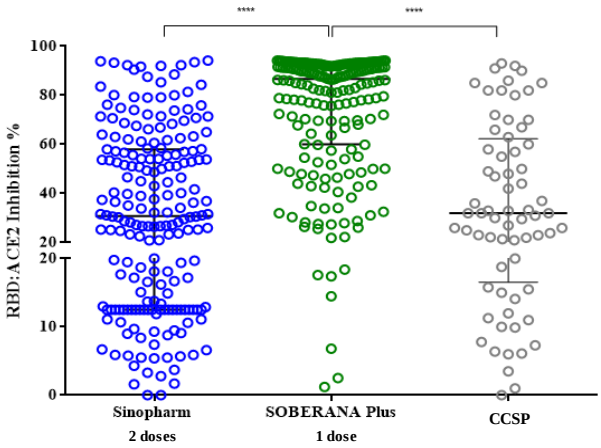


***Figure 3.*** *Capacity of anti-RBD IgG antibodies for inhibiting RBD:hACE2 interaction, as measured by competitive ELISA. % Inhibition of RBD:hACE2 interaction at 1/100 serum dilution. The median (25-75 percentile) is represented. The * represent significant differences, as indicated. CCSP: Cuban Convalescent Serum Panel.*

According to age groups; when evaluating the ability of antibodies to inhibit the RBD: ACE2 interaction after two doses in the group of 19 to 59 years, a median of 33.9% was observed, while when they receive the booster dose that value increases 2.6 times with

median of 89.1%. In vaccinated subjects older than 60 years, results are obtained that do not differ from those of the younger group with a median after two doses of 25.3% that increases when applying SOBERANA® Plus up to 83%, meaning an increase of 3.3 times.

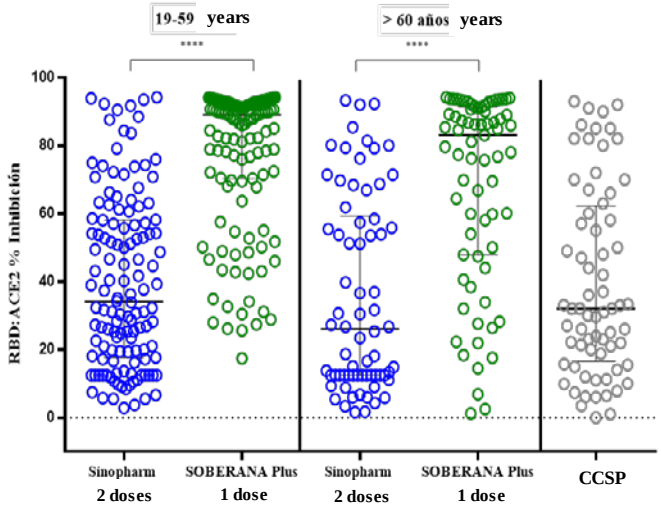


***Figure 4.*** *Capacity of anti-RBD IgG antibodies for inhibiting RBD:hACE2 interaction by age groups, as measured by competitive ELISA. % Inhibition of RBD:hACE2 interaction at 1/100 serum dilution. The * represent significant differences, as indicated. CCSP: Cuban Convalescent Serum Panel.*

For the evaluation of viral neutralization, a random subsample of 20 subjects was selected. A significant increase of neutralizing antibody titer is detected after the third dose, 19 times higher, as well as values significantly higher than the convalescent panel.

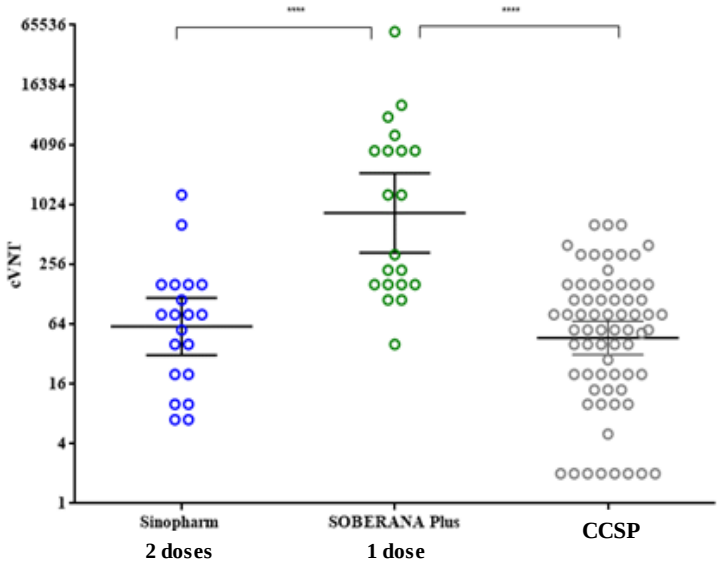


***Figure 5.*** *Conventional live-virus neutralization titre (cVNT). The * represent significant differences, as indicated. CCSP: Cuban Convalescent Serum Panel*

**Safety evidence of this heterologous combination of SINOPHARM and SOBERANA Plus.**

Safety evaluation was not planned as objective of this study, but the vigilance of adverse events was done by the pharmacovigilance system of the National Immunization Program. This information was included in this report due to its relevance.

When analyzing the adverse events reported during the administration of the heterologous scheme of BBIBP-CorV and SOBERANA® Plus, applied in subjects over 19 years of age, from the province of Cienfuegos, we can point out that only 19 adverse events (AE) were reported, after the first dose of the inactivated BBIBP-CorV vaccine, which represents 0.007% of subjects with AE and a rate of 7.0 x 100,000 applied doses. 87.4 were systemic and all fully recovered (Table 6).

No serious adverse events associated with the application of SOBERANA® Plus as a booster dose were reported.

***Table 1.*** *Frequency of adverse events following vaccination.*

| **Adverse events** | **No** |
|---|---|
| **Locals** | |
| Pain at the injection site | 3 |
| Erythema | 1 |
| **Systemic** | |
| AHT | 4 |
| Decay | 2 |
| headache | 2 |
| vagal crisis | 2 |
| Allergic reaction | 1 |
| Shaking chills | 1 |
| dizziness | 1 |
| Drowsiness | 1 |
| Acute seizure in epileptic patient | 1 |
| **Total** | **19** |

Conclusions:

- The heterologous booster vaccination with SOBERANA® Plus vaccine in BBIBP-CorV recipients was well tolerated and immunogenic.
- This study demonstrated the safety and immunogenicity of the SOBERANA® Plus vaccine as a booster dose of BBIBP-CorV, with the induction of high levels of specific functional antibodies.