



Open-label phase I/II clinical trial of SARS-CoV-2 receptor binding domain-tetanus toxoid conjugate vaccine (FINLAY-FR-2) in combination with receptor binding domain-protein vaccine (FINLAY-FR-1A) in children

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ABSTRACT

Objectives: To evaluate a heterologous vaccination scheme in children 3-18 years old (y/o) combining two SARS-CoV-2r- receptor binding domain (RBD)protein vaccines.

Methods: A phase I/II open-label, adaptive, and multicenter trial evaluated the safety and immunogenicity of two doses of FINLAY-FR-2 (subsequently called SOBERANA 02) and the third heterologous dose

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of FINLAY-FR-1A (subsequently called SOBERANA Plus) in 350 children 3–18 y/o in Havana Cuba. Primary outcomes were safety (phase I) and safety/immunogenicity (phase II) measured by anti-RBD immunoglobulin (Ig)G enzyme-linked immunoassay (ELISA), molecular and live-virus neutralization titers, and specific T-cells response. A comparison with adult immunogenicity and predictions of efficacy were made based on immunological results.

Results: Local pain was the unique adverse event with frequency >10%, and none was serious neither severe. Two doses of FINLAY-FR-2 elicited a humoral immune response similar to natural infection; the third dose with FINLAY-FR-1A increased the response in all children, similar to that achieved in vaccinated young adults. The geometric mean (GMT) neutralizing titer was 173.8 (95% confidence interval [CI] 131.7; 229.5) vs Alpha, 142 (95% CI 101.3; 198.9) vs Delta, 24.8 (95% CI 16.8; 36.6) vs Beta and 99.2 (95% CI 67.8; 145.4) vs Omicron.

Conclusion: The heterologous scheme was safe and immunogenic in children 3–18 y/o.

Trial registry: <https://rpec.sld.cu/trials/RPECE00000374>

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Introduction

Protecting children against COVID-19 is pivotal for controlling virus dissemination and reducing disease incidence. COVID-19 cases and hospitalizations among children and adolescents, firstly driven by the Delta variant and recently by Omicron, have risen sharply, even in countries with high adult vaccination coverage (Delahoy et al., 2021; Elliott et al., 2022). This context has accelerated the clinical trials of anti-SARS-CoV-2 vaccines for children (Ali et al., 2021; Frenck et al., 2021; Han et al., 2021; Wallace et al., 2021; Walter et al., 2021; Xia et al., 2022).

For more than 30 years, the Finlay Vaccine Institute has produced tetanus toxoid-conjugated vaccines applied to children worldwide; their safety has been extensively proven through hundreds of millions of doses (Huang and Wu, 2010; Verez-Bencomo et al., 2004). FINLAY-FR-2 (also called SOBERANA 02) immunogen is an anti-SARS-CoV-2 recombinant receptor binding domain (RBD) conjugated to tetanus toxoid (Valdes-Balbin et al., 2021a, 2021b). It is the unique conjugate vaccine in World Health Organization's vaccines pipeline (World Health Organization, 2021). T-cell epitopes present in tetanus toxoid were expected to promote RBD-specific B- and T-cell memory, high affinity and longstanding RBD IgG antibodies.

SOBERANA 02 has proved its safety and immunogenicity in adults 19–80 years old (y/o); after two doses, its efficacy was 69.7%. Combined with the third dose of FINLAY-FR-1A (also called SOBERANA Plus) (recombinant RBD dimer vaccine) in a three-dose heterologous scheme, efficacy increased to 92.0% (Eugenia-Toledo-Romani et al., 2021, 2022a, 2022b). In August 2021, the Cuban Regulatory Authority granted their emergency use authorization in adults, being since then extensively applied nationally for preventing COVID-19 in Cuba (Cuban and National Regulatory Agency, 2021).

Here, we report the results of an open-label phase I/II clinical trial in children 3–18 y/o to evaluate the safety and immunogenicity of two doses of FINLAY-FR-2 and the third dose of FINLAY-FR-1A. We avoided a placebo-controlled trial in this age group due to ethical concerns (Dal-Ré and Caplan, 2021); alternatively, a recommended comparison (or immunobridging) with an adult's immunogenicity was established (US Food and Drug Administration [FDA], 2021) and the clinical efficacy was estimated based on immunological results.

Method

Study design

We designed a phase I/II study, open-label, adaptive and multicenter to evaluate the safety, reactogenicity, and immunogenic-

ity of two doses of FINLAY-FR-2 and a third heterologous dose of FINLAY-FR-1A in children (3–11 y/o) and teenagers (12–18 y/o). Two interim analyses would decide interruption/continuation of the study, depending on serious adverse events (AEs) during phase I.

Phase I was conceived in a two-step, incorporating firstly 25 children 12–18 y/o (sequence 1). The first interim report (no serious AE detected) 7 days after their vaccination allowed incorporating 25 children 3–11 y/o (phase I, sequence 2 and starting phase II in 12–18 y/o [n = 150]). A second interim report 7 days after sequence 2 (no serious AE detected) allowed starting phase II in children 3–11 y/o (n = 150). (Figure 1). Detailed information on trial sites is presented in Supplementary Material I.

Children were recruited at the community level across the primary health system by medical doctors. They were included following a physical examination, parent interview, and phase I clinical laboratory assays. Key inclusion criteria were weight-height nutritional assessment, physical examination without alterations, clinical laboratory results within the range of reference values (only phase I), and microbiology laboratory tests. Key exclusion criteria were any acute infection, previous or current history of SARS-CoV-2 infection, and being a contact of a positive COVID-19 case. A detailed description of selection criteria appears in Supplementary Material II.

Ethical issues

The trial was approved by the Ethical Committee at the “Juan Manuel Marquez” Pediatric Hospital and endorsed by the Cuban National Pediatric Group. The Cuban National Regulatory Agency (Centre for State Control of Medicines and Medical Devices, Cuban and National Regulatory Agency) approved the trial (June 10, 2021, Authorization Reference: 05.010.21BA).

Independent Data Monitoring Committees formed by five external members specialized in pediatric clinical practice, immunology, and statistics were in charge of two interim analyses during phase I.

The trial was conducted according to the Declaration of Helsinki, Good Clinical Practice, and the Cuban National Immunization Program. During recruitment, the medical investigators provided to the parents, both orally and written, all information about the vaccine and its potential risks and benefits. Written informed consent was obtained from both parents; children ≥over 12 y/o should assent. The decision to participate was not remunerated.

The National Clinical Trials Coordinating Centre (CENCEC) was responsible for monitoring the trial in terms of adherence to the protocol, Good Clinical Practice, and data accuracy.

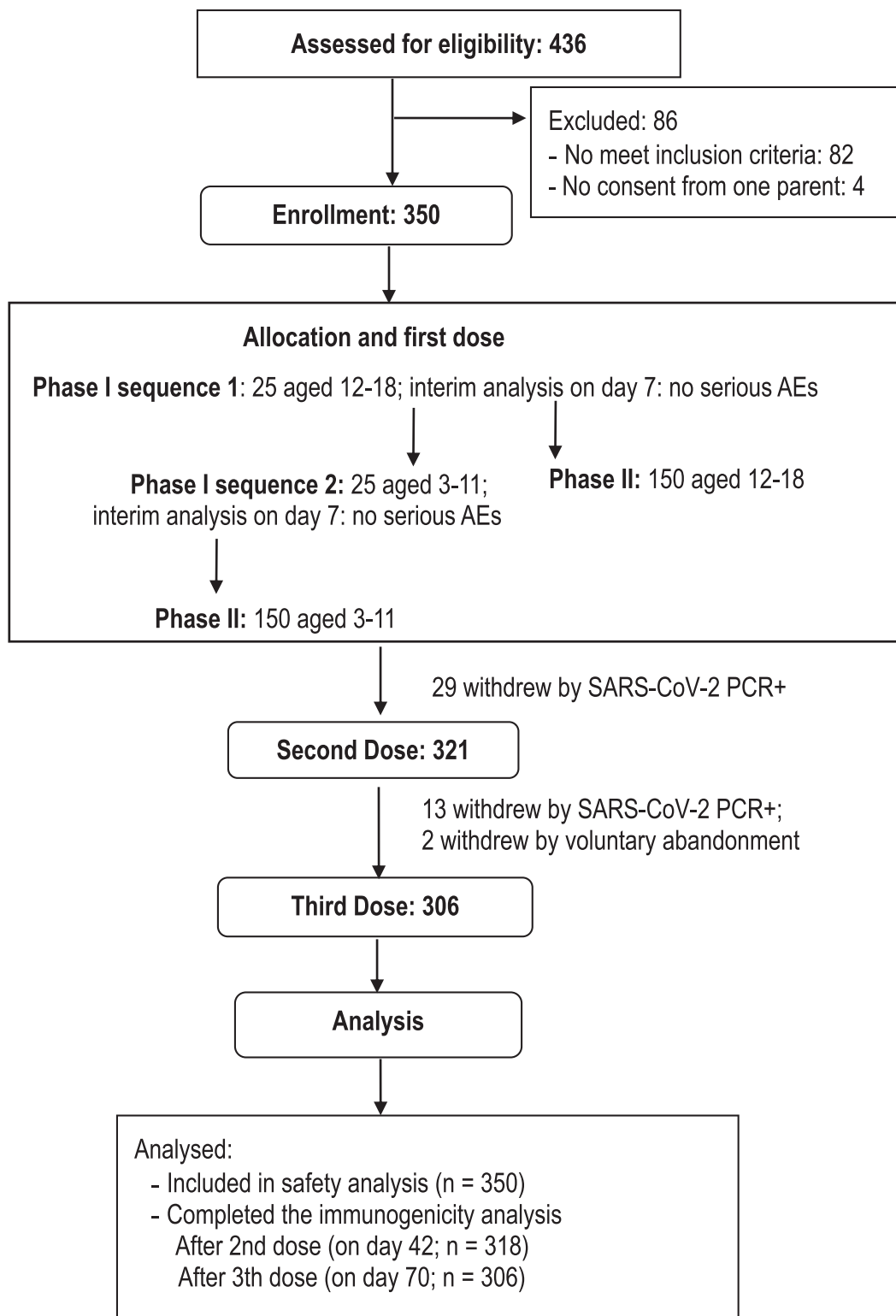


Figure 1. Flow chart: recruitment, inclusion, vaccination and follow-up of 3-18 years old children in phase I/II trial. AE, adverse event; PCR, polymerase chain reaction.

Trial registry: RPCEC00000374 (Cuban Public Registry of Clinical Trials and World Health Organization International Clinical Registry Trials Platform) ([International register clinical trials, 2021](#)).

Products under evaluation

FINLAY-FR-2 (RBD chemically conjugated to the carrier protein tetanus toxoid) and FINLAY-FR-1A (RBD dimer), adjuvanted in alu-

mina hydroxide, were produced at the Finlay Vaccine Institute and the Centre for Molecular Immunology, in Havana, Cuba, under Good Medical Practice conditions. Both are subunit vaccines-based SARS-CoV-2 RBD, sequence Arg319-Phe541, produced in genetically modified Chinese hamster ovary (CHO) cells. Formulations are detailed in Supplementary Material III-Table S1.

Product batches used: FINLAY-FR-2 (E1002S02X, E1002S02); FINLAY-FR-1A (E1001SP).

Procedures

Reverse transcriptase-polymerase chain reaction (PCR) SARS-CoV-2 was performed in all participants at least 72 hours before each dose. Participants with negative PCR results received the vaccine by intramuscular injections in the deltoid region. *Immunization schedule*: two doses of FINLAY-FR-2 and a heterologous third dose of FINLAY-FR-1A 28 days apart (immunization on days 0, 28, 56). After each immunization, participants were on-site evaluated for 1 hour. Medical control visits were planned at 24, 48, and 72 hours and on days 7, 14, and 28 after each dose. AEs were registered by parents daily. Serum samples were collected on day 0 (before vaccination) and 14 days after the second and third doses (days 42 and 70). Peripheral blood mononuclear cells were obtained before vaccination and after the third dose (day 70) in a participant subset of 45 children randomly selected in each age subgroup.

Outcomes

Primary outcomes. Phase I: occurrence of serious AEs, measured daily for days after each dose. Phase II: Percentage of subjects with seroconversion ≥ 4 -fold increase of immunoglobulin (Ig)G anti-RBD over pre-immunization, on days 42 and 70.

Secondary outcomes. Phase I and phase II: Solicited local and systemic AEs, measured during 7 days after each dose; unsolicited AEs, measured 28 days after each dose; neutralizing antibody titers (on days 42 and 70, on a sample subset), inhibition of RBD-human angiotensin I-converting enzyme 2 (hACE2) interaction (on days 42 and 70). Phase II: Occurrence of serious AEs, measured 28 days after each dose. Outcomes are detailed in Supplementary Material III).

Outcomes and safety assessments are detailed in Supplementary Materials IV and V.

Immunogenicity assessment

Immunogenicity was evaluated by: (i) quantitative ultramicro enzyme-linked immunoassay (ELISA) (UMELISA SARS-CoV-2 anti-RBD); (ii) competitive ELISA determined the inhibitory capacity of antibodies for blocking the RBD-hACE2 interaction, expressed as percentage inhibition and molecular virus neutralization titer (mVNT₅₀); (iii) conventional virus neutralization titer (cVNT₅₀) vs D614G, Alpha, Beta, Delta, and Omicron variants; (iv) RBD-specific T-cells response producing interferon (IFN)- γ and interleukin (IL)-4. Immunogenicity assessment and techniques are described in Supplementary Material VI. All immunological evaluations were performed by external laboratories from the Centre for Immunoassays, the Centre of Molecular Immunology, and the National Civil Defense Research Laboratory. The T-cells response was evaluated at Finlay Vaccine Institute. A detailed description of immunogenicity assessments and techniques is described in Supplementary Material VI.

Children's convalescent serum panel

A Cuban children's convalescent serum panel was made with sera from 82 patients (3-18 y/owho) who recovered from COVID-

Table 1
Demographic characteristics of subjects included in the clinical trial.

	Age groups		
	3-11 years	12-18 years	Total 3-18 years
N	175	175	350
Sex			
Female	80 (45.7%)	83 (47.4%)	163 (46.6%)
Male	95 (54.3%)	92 (52.6%)	187 (53.4%)
Skin color			
White	122 (69.7%)	116 (66.3%)	238 (68.0%)
Black	9 (5.1%)	11 (6.3%)	20 (5.7%)
Multiracial	44 (25.1%)	48 (27.4%)	92 (26.3%)
Age (years)			
Mean (SD)	7.4 (2.5)	15.1 (2.1)	11.3 \pm 4.5
Median (IQR)	8.0 (5.0)	15.0 (4.0)	11.5 \pm 7.0
Range	3; 11	12;18	3-18
Weight (kg)			
Mean (SD)	29.4 (10.1)	54.7 (9.0)	42.0 \pm 15.9
Median (IQR)	27.5 (14.0)	55.0 (13.0)	43.0 \pm 27.7
Range	13.0; 58.0	32.0; 80.0	13.0; 80.0
Height (cm)			
Mean (SD)	129.1 (17.2)	164.3 (9.6)	146.7 \pm 22.5
Median (IQR)	131.0 (26.0)	164.0 (13.0)	151.0 \pm 34.0
Range	92; 172	142; 190	92-190
Body mass index (kg/m²)			
Mean (SD)	17.0 (2.0)	20.2 (2.3)	18.6 \pm 2.7
Median (IQR)	16.7 (2.7)	19.9 (3.8)	18.3 \pm 4.1
Range	13.2; 22.8	14.6; 25.5	13.2-25.5

Data are n (%) unless otherwise specified.

Range presented as minimum; maximum.

Abbreviations: IQR, interquartile range; SD, standard deviation

19. Detailed information about panel composition and immune characterization is presented in Supplementary Material VII.

Statistical analysis

For phase I, the calculation of sample size was done considering a 2-sided 95% confidence interval (CI) for one proportion with a width equal to 0.09 to estimate a serious AE rate of <1%. For phase II, a similar method was used to estimate a seroconversion of around 50%, with a lower bound of the CI >30% (trial hypothesis) and a dropout of 20%. This resulted in a sample size of 350 subjects (including subjects from phase I). Detailed statistical tools, procedures, and definitions are presented in Supplementary Material VIII.

Results

Figure 1 and Table 1 describe the study design and demographic characteristics of the participants. From June 11 to July 14, 2021, 426 children (3-18 y/o) were recruited, 350 that accomplished the selection criteria were included, and 306 completed the study. There was a balanced ratio of sex and ethnicity; the mean age was 11.3 years (SD 4.5).

Phase I started by vaccinating 25 children 12-18 y/o with FINLAY-FR-2; the first interim analysis was done 7 days after vaccination, indicating the absence of serious AEs. In consequence, the trial proceeded to phase I sequence 2, incorporating 25 children aged 3-11 and 150 children aged 12-18 of phase II. The second interim analysis showed no serious AE in children 3-11 y/o (sequence 2); the trial completed phase II, vaccinating 150 children 3-11 y/o with FINLAY-FR-2 first dose.

During the vaccination scheme, 86 children (53.1%) suffered at least one AE; the frequency was higher (60%) in teenagers than in young children (46.3%). Severe and serious vaccine-associated AEs did not occur (Table 2). Local AE predominated; the most common was local pain (47.7%), and all others had frequencies <5%; only 1.1% reported fever (Table 3). More than 90% of AEs were

Table 2
General characteristics of AEs.

	Age groups		
	3-11 years	12-18 years	Total
N	175	175	350
Subjects with some AE	81 (46.3%)	105 (60.0%)	186 (53.10%)
Subjects with some VAAE	76 (43.4%)	101 (57.7%)	177 (50.6%)
Subjects with some serious AE	0 (0.0%)	1 (0.6%) ^a	1 (0.3%)
Subjects with some serious VAAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with some severe AE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with some severe VAAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total of Adverse Events	141	182	323
VAAE	126 (89.4%)	160 (87.9)	286 (88.5%)
Serious VAAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe VAAE	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data are n (%).

Abbreviations: AE, adverse event; VAAE, vaccine-associated AE.

^a Serious AE: Dengue required hospitalization.**Table 3**
Frequency of solicited AEs.

	Age groups		
	3-11 years	12-18 years	Total
N	175	175	350
Subjects with some AE	81 (46.3%)	105 (60.0%)	186 (53.10%)
Subjects with solicited local AE			
Any	74 (42.3%)	98 (56.0%)	172 (49.1%)
Local pain	69 (39.4%)	98 (56.0%)	167 (47.7%)
Swelling	9 (5.1%)	2 (1.1%)	11 (3.1%)
Local warm	4 (2.3%)	0 (0.0%)	4 (1.1%)
Erythema	5 (2.9%)	1 (0.6%)	6 (1.7%)
Induration	5 (2.9%)	1 (0.6%)	6 (1.7%)
Subjects with solicited systemic AE			
Any	5 (2.9)	4 (2.3)	9 (2.6)
General discomfort	1 (0.6%)	3 (1.7%)	4 (1.1%)
Fever (≥ 38 °C)	2 (1.1)	1 (0.6)	3 (0.9)
Low-grade fever (<38 °C)	4 (2.3)	1 (0.6)	5 (1.4)

Data are n (%) unless otherwise specified.

AE, adverse event.

classified as mild and lasted ≤ 72 hours, and 88.5% were associated with vaccination (Table 3, Supplementary Material IX-Table S2). AEs were more frequent after the first dose than after the second and third doses (Supplementary Material IX-Table S3). Few unsolicited AEs were recorded (Supplementary Material IX-Table S4). Hematology and blood chemistry were studied on days 0 (before the first dose), 7, and 70 (14 days after the third dose). Data were separately evaluated in two age groups (3-11 y/o, N=25, and 12-18 y/o, N=24, from phase I). No clinically relevant changes were observed in hematology and blood chemistry analyses.

Before vaccination, 97.1 % of children were negative for anti-RBD antibodies; median anti-RBD IgG was 1.95 UA/ml (25th-75th percentile 1.95; 1.95). Two doses of FINLAY-FR-2 induced seroconversion in 96.2% of participants (95% CI 93.5; 98.0) and satisfied the trial hypothesis (>50% of seroconversion with a lower boundary of the 2-sided 95% CI >0.3) (Table 4). The global seroconversion index was 27.8; the median anti-RBD IgG was 57.0 UA/ml (25th-75th percentile 29.8; 153.4 (Table S5). By age subgroup, seroconversion was 99.4% (95% CI 96.5; 99.9) in children 3-11 y/o and 93.1% (95% CI 88.0; 96.5) in 12-18 y/o (Supplementary Material IX-Table S5). The heterologous third dose with FINLAY-FR-1A increased seroconversion to 100% and seroconversion index to 154.5; anti-RBD IgG titers also increased significantly ($P < 0.005$) to 325.7 UA/ml (25th-75th percentile 141.5; 613.8) (Table 4). Specific antibody response was higher than the elicited by natural infection, evaluated in Cuban children's convalescent panel (anti-RBD IgG median 11.5; 25th-75th percentile 5.3; 24.2).

The capacity of anti-RBD IgG for blocking RBD-hACE2 interaction after two doses of FINLAY-FR-2 was 67.4 % (25th-75th percentile 42.1; 86.9), and the mVNT₅₀ was 198.5 (95% CI 168.4; 233.9); both increased significantly ($P < 0.005$) after the third dose to 92.4 % (25th-75th percentile 88.3; 93.5) and 1261 (95% CI 1105.5; 1438.8) respectively (Table 4). These values were higher among the younger children (3-11 y/o) after the second dose but were similar in both age subgroups after the third dose (Supplementary Material IX-Table S5). After two and three doses, mVNT₅₀ was higher than after natural infection.

After two doses of FINLAY-FR-2, the neutralizing titer vs D614G variant was higher (geometric mean titer [GMT] 26.4; 95% CI 20.2; 34.5) than the children convalescent panel value (GMT 9.2; 95% CI 6.8; 12.5); and the third dose significantly ($P < 0.005$) boosted the response to GMT 158.4 (95% CI 123.0; 204.0) (Table 4). The neutralizing titer vs the variants Alpha, Beta, and Delta was evaluated in 48 children; 100% had neutralizing antibodies vs Alpha and Delta, and 97.9% vs Beta. cVNT₅₀ GMT was 173.8 (95% CI 131.7; 229.5) vs Alpha, 142 (95% CI 101.3; 198.9) vs Delta, and 24.8 (95% CI 16.8; 36.6) vs Beta; (a 2.2-fold decrease for Delta and 7.0-fold decrease for Beta, compared with D614G). Additionally, a subset of 33 paired samples was also evaluated vs Omicron variant, showing a neutralization titer of 99.2 (95% CI 67.8; 145.4) (Table 5).

There was a good correlation among all humoral immunological variables. Predictive cut-off for attaining cVNT₅₀ over 50 was estimated by receiver operating characteristic (ROC) curve as: 192.2 AU/ml for IgG concentration, 87.1% for the inhibition of RBD:hACE2 and 427 for mVNT₅₀ (Supplementary Material X-Table S6, Figure S1).

RBD-specific T-cell response in a subset of 45 participants fully vaccinated was determined by measuring IFN- γ and IL-4 expression in peripheral blood mononuclear cells. The number of IFN- γ and IL-4 secreting cells was statistically higher ($P < 0.001$) than their baseline levels (Figure 2).

The safety and immune response in children were compared with young adults (aged 19-39 y/o) vaccinated in phase I and phase II studies with the same vaccine regimen, as recommended by the FDA (2021). Safety profile was similar in both (Supplementary Material X-Tables S7, S8, Figure S2). An immunobridging analysis was performed for anti-RBD IgG, mVNT₅₀, and cVNT₅₀ between children and young adults. IgG elicited after two doses of FINLAY-FR-2 was 57.0 UA/ml (25th-75th percentile 29.8; 153.4), while for young adults, it was 46.4 (25th-75th percentile 17.4; 108.8); after the heterologous third dose of FINLAY-FR-1A these values increased to 325.7 (25th-75th percentile 141.5; 613.8) in children and 228.0 (25th-75th percentile 95.8; 394.3) in young adults. mVNT₅₀ was 198.5 (95% CI 168.4; 233.9) in children after the second dose

Table 4
Humoral immune response induced after two doses of FINLAY-FR-2 and the third heterologous dose with FINLAY-FR-1A.

		Age group 3-18 y/o		Cuban children's convalescent serum panel
		Post-2 nd dose	Post-3 rd dose	
Anti-RBD IgG	N	318	306	82
seroconversion rate	N (%)	305/317 (96.2)	305/305 (100.0) ^a	ND
Anti-RBD IgG AU/ml	95% CI	93.5; 98.0	99.8; 100.0	
Seroconversion index	Median	57.0	325.7 ^a	11.5
	25 th -75 th	29.8; 153.4	141.5; 613.8	5.3; 24.2
RBD:hACE2 Inh%	Median	27.8	154.5 ^a	ND
	25 th -75 th	14.3; 69.0	67.2; 260.9	
mVNT ₅₀	Median	67.4	92.4 ^a	20.8
	25 th -75 th	42.1; 86.9	88.3; 93.5	10.9; 40.8
cVNT ₅₀ vs D614G	GMT	198.5	1261.2 ^a	35.2
	95% CI	168.4; 233.9	1105.5; 1438.8	25.3; 48.9
cVNT ₅₀ vs D614G	N	123	131	70
	GMT	26.4	158.4 ^a	9.2
	95% CI	20.2; 34.5	123.0; 204.0	6.8; 12.5

Abbreviations: Anti-RBD IgG seroconversion rate, % of subjects with seroconversion (95% CI); AU/ml, anti-RBD IgG concentration expressed in arbitrary units/ml; CI, confidence interval; cVNT₅₀: conventional live-virus neutralization titer; GMT, geometric mean titer; Ig, immunoglobulin; mVNT₅₀: molecular virus neutralization titer; ND, not determined; RBD, receptor binding domain; RBD:hACE2 Inh%: RBD:hACE2 inhibition % at a serum dilution 1/100; Seroconversion index: fold increase of IgG concentration respect to baseline (median; 25th-75th percentile).

Footnote: t₀ or baseline anti-RBD IgG was 1.95 (25th-75th percentile: 1.95; 1.95).

^a P <0.005 vs post-2nd dose McNemar test (anti-RBD IgG seroconversion %), Wilcoxon Signed Ranks test (anti-RBD IgG AU/ml, RBD:hACE2 Inh%) or paired Student's t-test (mVNT₅₀, cVNT₅₀, log-transformed).

Table 5
Conventional live-virus neutralization titers against SARS-CoV-2 variants Alpha, Delta, Beta and Omicron.

		D614G	Alpha	Delta	Beta	Omicron BA.1
cVNT ₅₀	N	48	48	48	48	
	GMT	173.8	142.0	76.8 ^a	24.8 ^a	
	95% CI	131.7; 229.5	101.3; 198.9	54.8; 107.7	16.8; 36.6	
cVNT ₅₀	N	33	33	33	33	33
	GMT	169.8	126.6 ^a	72.4 ^a	19.4 ^a	99.2 ^a
	95% CI	120.2; 239.7	86.7; 184.8	47.4; 110.6	12.7; 29.7	67.8; 145.4

Abbreviations: CI, confidence interval; cVNT₅₀: conventional live-virus neutralization titer; GMT, geometric mean titer.

Sera from 48 children vaccinated with complete schedule (two doses FINLAY-FR-2 + one dose FINLAY-FR-1A, 28 days apart) were evaluated against D614G, Alpha, Delta and Beta variants. Of them, 33 paired samples were evaluated also vs Omicron.

^a P <0.005 paired Student's t-test (cVNT₅₀, log-transformed) respect to D614G variant.

and 1261.2 (95% CI 1105.5; 1438.8) after the third; in young adults were 94.9 (95% CI 75.0; 120.2) and 503.7 (95% CI 432.6; 586.6) after two and three doses (Figure 3). We found significant differences (P <0.05) for IgG and mVNT₅₀ between 3-18 y/o children and 19-39 y/o young adults; higher values were obtained in children after both the second and the third dose. Viral neutralization titers after the second dose were measured at different time points in children and young adults (on day 42 in children and day 56 in young adults), making their comparison only approximate.

The non-inferiority analysis was performed with cVNT₅₀ data, following the FDA's (2021) recommendation. After three doses (on day 70), cVNT₅₀ in children was 158.4 (95% CI 123.0; 204.0) and 122.8 (80.2; 188.0) for young adults (n = 43, data available) (Figure 3). The immune response in 3-18 y/o, as well as in age subgroups 3-11 y/o and 12-18 y/o, was non-inferior to that observed in 19-39 y/o young adults. The cVNT₅₀ GMT ratio 14 days after the third dose was 1.25 (95% CI 0.77; 2.02) (Table 6) for children 3-18 y/o, respectively, to adults, which met the non-inferiority criterion (i.e., a lower boundary of the two-sided 95% CI of >0.67). In addition, both age subgroups (3-11 y/o and 12-18 y/o) met the non-inferiority criterion.

Based on immunogenicity data of vaccinated children and the immune response to natural infection (children convalescent panel), a prediction of clinical efficacy was estimated through a linear regression model. By using cVNT₅₀ as the predictive variable, the estimated efficacy vs D614G is 91.3% (95% CI 84.6; 95.1)

after two doses and 97.4 % (95% CI 91.5; 99.2) after three doses (Figure 4).

Discussion

This study describes, for the first time, the safety and immunogenicity in children 3-18 y/o of two doses of FINLAY-FR-2, followed by a third heterologous dose of FINLAY-FR-1A. The frequency of local and systemic AE was 49.0% and 2.6%, respectively, lower than after messenger RNA (mRNA) COVID-19 vaccination. After two doses, BNT162b2 reported 86.0% and 66.0 of children 12-15 y/o with local and systemic AEs, while mRNA-1273 reported 94.2% and 68.3% (aged 12-17 y/o), respectively. In our study, local pain was reported by 51.4% of children aged 12-18 y/o after the first dose, 17% after the second, and 17.3% after the third dose. BNT162b2 and mRNA-1273 vaccines in adolescents reported 86.0% and 94.2% with local pain after the first dose; and 79.0% and 92.4% after the second, respectively. FINLAY-FR-2 and FINLAY-FR-1A caused general discomfort (the most frequent systemic AE) only in 1.7% of children 12-18 y/o, while mRNA vaccines provoked fatigue, headache, chills, muscle pain, or fever in 10-68.5% of adolescents (Ali et al., 2021; Frenck et al., 2021). In children 3-11 y/o, local pain was the unique AE with frequency >10% during this study; children 5-11y/o vaccinated with BNT162b2 reported local pain (74.0%), redness (19.0%), swelling (15.0%), fatigue (39.0%), and headache (28.0%) (Walter et al., 2021). Myocarditis and pericarditis have been reported in ado-

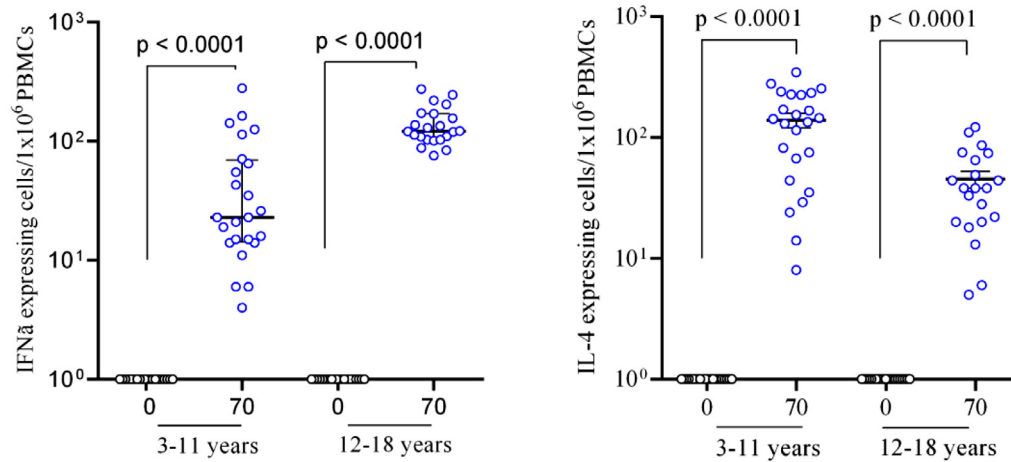


Figure 2. IFN- γ - and interleukin-4-secreting cells in peripheral blood mononuclear cells stimulated with receptor binding domain. Children 3-11 (N=24) and 12-18 years old (N=21) received two doses (on days 0, 28) of FINLAY-FR-2 and a heterologous third dose (on day 56) of FINLAY-FR-1A. P-value represents the statistic differences as indicated. IFN, interferon; PBMC, peripheral blood mononuclear cells.

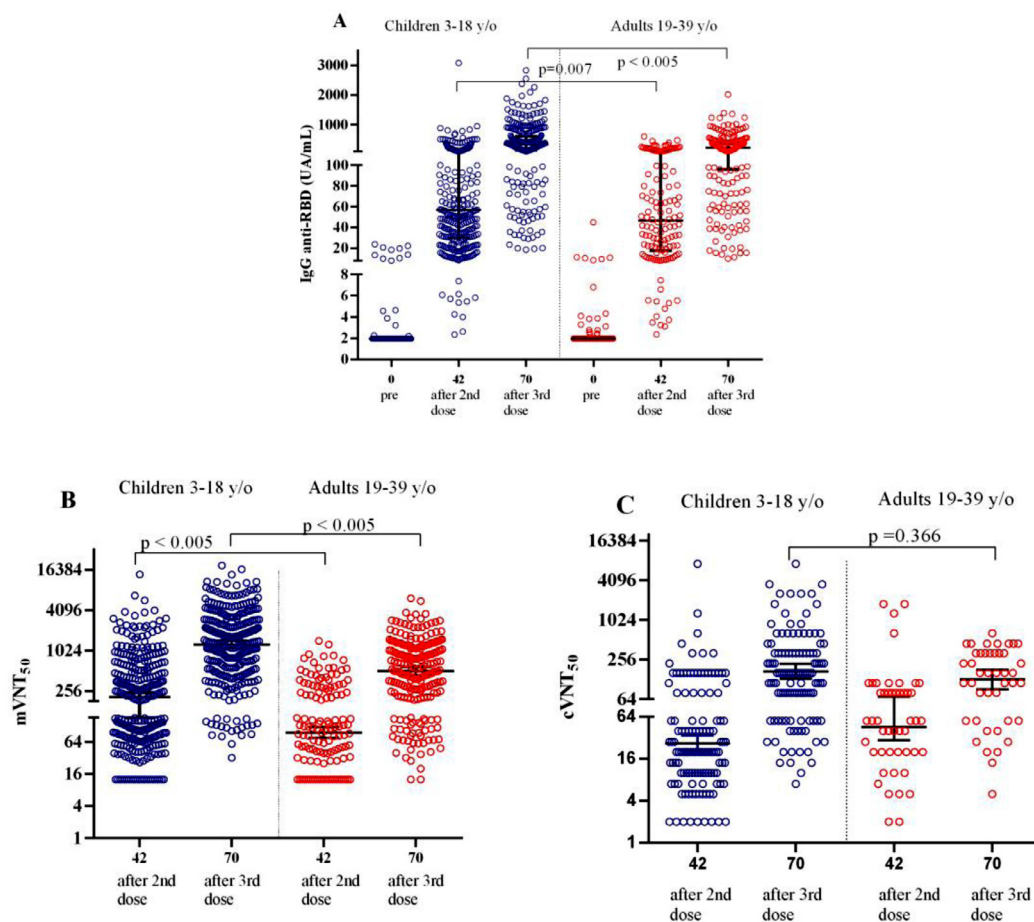


Figure 3. Immunobridging comparison of humoral immune response elicited in children (3-18 y/o) respect to young adults (19-39 y/o from phase I and II clinical trials) after two doses of FINLAY-FR-2 (day 42) and the third dose of FINLAY-FR-1A (day 70). (a) anti-RBD IgG median (25th-75th percentile); (b) mVNT₅₀ GMT (95% CI); (c) cVNT₅₀ GMT (95% CI). Bleeding was on day 42 and 70 (14 days after the second and third dose), except for cVNT₅₀ adults after the second dose was on day 56. Mann-Whitney U test (anti-RBD IgG AU/ml) or Student's *t*-test (mVNT₅₀, cVNT₅₀, log-transformed). P-value represents the statistic differences as indicated. cVNT₅₀, conventional live-virus neutralization titer; GMT, geometric mean titer; Ig, immunoglobulin; mVNT₅₀, molecular virus neutralization titer; RBD, receptor binding domain; y/o, years old.

Table 6
Immunobridging of cVNT₅₀ in children and young adults after heterologous scheme (two doses of FINLAY-FR-2 and the third heterologous dose of FINLAY-FR-1A)

Age group	No. of participants	cVNT ₅₀ GMT (95% CI)	Geometric mean ratio (95% CI) vs 19 to 39 y/o
19-39 y/o	43	127.0 (89.6; 179.80)	–
3-18 y/o	131	158.4 (123.0; 204.0)	1.25 (0.77; 2.02)
3-11 y/o	66	181.6 (120.6; 273.3)	1.43 (0.80; 2.54)
12-18 y/o	65	137.9 (101.8; 186.9)	1.08 (0.68; 1.73)

Abbreviations: CI, confidence interval; cVNT₅₀: conventional live-virus neutralization titer; GMT, geometric mean titer; y/o, years old. GMT and two-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student's *t*-distribution). The geometric mean ratio and two-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (in children/adolescents cohorts minus the 19-39-y/o cohort) and the corresponding CIs (based on the Student's *t*-distribution). The non-inferiority criterion was met, since the lower boundary of the two-sided CI for the geometric mean ratio was greater than 0.67.

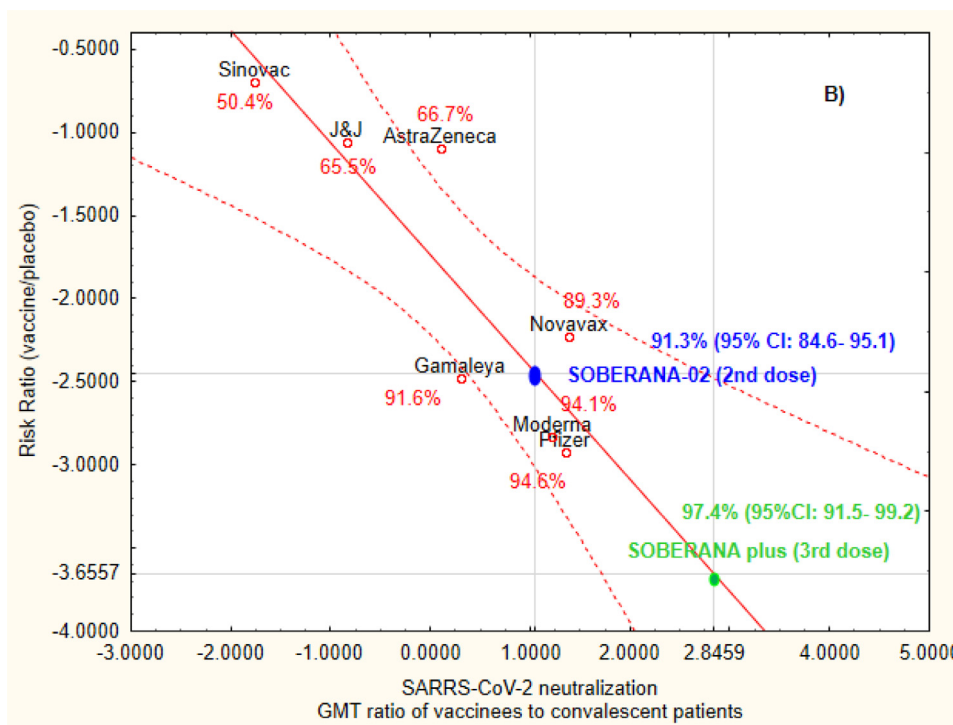


Figure 4. Prediction of clinical efficacy in children from the correlation between antibody responses and efficacy rate. Panels display correlation of cVNT₅₀ neutralization and ratios, respectively for seven vaccines in adults; two doses of FINLAY-FR-2 (represented as SOBERANA 02) and the heterologous three doses adding FINLAY-FR-1A (represented as SOBERANA Plus) in children. The y-axis is estimated log risk ratio reported on the vaccine efficacy scale. The x-axis is log ratio of the peak geometric mean neutralization at 7–28 days post-vaccination, relative to human or children convalescent sera. CI, confidence interval; cVNT₅₀: conventional live-virus neutralization titer; GMT, geometric mean titer.

lescents after mRNA COVID-19 vaccination (Marshall et al., 2021; Oster et al., 2022); these AEs were not observed here.

The comparison of the humoral immune response elicited by vaccination to the response elicited by natural infection has been a useful tool for the development of several anti-SARS-CoV-2 vaccines (Keech et al., 2020; Yang et al., 2021). Two shots of FINLAY-FR-2 every 28 days in children induced a robust humoral response, with higher levels of antibodies and a similar neutralizing capacity of the response elicited by natural infection. The third dose of FINLAY-FR-1A boosted both the production of antibodies and their neutralizing capacity, surpassing the immune response in convalescent children, as had been previously observed in clinical trials in adults (Eugenia-Toledo-Romaní et al., 2022a, 2022b).

The induction of specific T-cell response is critical for the protection of viral infections. The heterologous three-dose schedule in children developed a balanced activation of IFN- γ and IL-4-secreting cells from peripheral blood mononuclear cells (PBMC),

indicating a mixed Th1/Th2 response, as reported in adults after the same vaccination scheme (Eugenia-Toledo-Romaní et al., 2022a).

The SARS-CoV-2 variants of concern Alpha, Beta, Delta, and recently Omicron, have modified the pandemic landscape worldwide (Fontanet et al., 2021). Here, we report the capacity of anti-RBD antibodies for neutralizing Alpha, Beta, Delta, and Omicron variants, with a fold-reduction of 2.2 for Delta and 7.0 for Beta compared with D614G, as we found in adults (Eugenia-Toledo-Romaní et al., 2022b). In an independent study from the “Pedro Kourí” Tropical Medicine Institute in Havana, sera from 20 adults (vaccinated with the same vaccine regimen) neutralized the Omicron variant (Carles, 2022; Portal-Miranda, 2022).

We conducted this clinical trial during the Delta wave, the worst period of the Cuban epidemic (Rodríguez, 2021); in such a context and due to ethical reasons, a placebo-controlled clinical trial was not ethical, and this is the main limitation of the

study. Lacking a control group, two analytical tools complemented the study: immunobridging with the immune response in young adults previously vaccinated during clinical trials with the same vaccination schedule (no concurrent reference population) as recommended by the FDA (2021); and prediction of clinical efficacy based on immunological response (Khoury et al., 2021; Kristen et al., 2021). First, we found a non-inferior response for the GMT ratio of SARS-CoV-2 cVNT₅₀ after the three-dose scheme in participants 3–11 and 12–18 y/o relative to a 19–39 y/o reference population (no concurrent). The comparison met the non-inferiority criterion with a ratio of 1.43 (95% CI 0.8–2.54) for 3–11 y/o and 1.08 (95% CI 0.68–1.73) for 12–18 y/o, satisfying the FDA (2021) recommendations (a lower boundary of the 2-sided 95% CI of >0.67). Similar analyses have been reported by BNT162b2 and mRNA-1273 vaccines using 19–25 y/o as reference population (Walter et al., 2022; Ali et al., 2021). Based on published results, we considered young adults as immunocompetent for up to 39 years (Lopez-Sejas et al., 2016; Thapa and Farber, 2019; Ventura et al., 2017); this increased the number of cVNT₅₀ data for comparison in the reference population.

Second, a prediction of clinical efficacy based on immunological response has been advanced for other vaccines (Khoury et al., 2021; Kristen et al., 2021). Using this model, for adults aged 19–80 y/o, we anticipated a clinical efficacy between 58% and 87% after the first two doses and between 81% and 93% after the three-dose scheme vs the D614G variant (Eugenia-Toledo-Romani et al., 2022b). These results were confirmed during a phase III clinical trial reporting a 69.7% efficacy for the two-dose schedule of FINLAY-FR-2 and 92.0% for the heterologous three-dose schedule during the Beta period (Eugenia-Toledo-Romani et al., 2021). Here, the model predicts 91.3% clinical efficacy after two doses of FINLAY-FR-2 and 97.4% after the third dose of FINLAY-FR-1A in children vs the D614G strain.

Starting vaccination of children at 2 y/o is key for controlling the pandemic, reducing transmission, and reducing the emergence of new variant of concerns (Petersen and Buchy, 2021). The safety and immunological results reported here supported the emergency use authorization of FINLAY-FR-2 and FINLAY-FR-1A as a heterologous scheme for children 2–18 y/o. A massive immunization campaign started on September 5, 2021, fully vaccinating 1.8 million Cuban children (96% of the 2–18 y/o Cuban population [Augustin, 2022; Reed, 2022]). These results support public health vaccination strategies, providing children as young as 2 years with a safe and effective vaccine scheme to prevent COVID-19.

Authors contributions statement

D.G.R, Y.V.B, R.P.G, and V.V.B conceptualized the study. R.P.G, Y.R.D, C.R.I, L.C.H, M.P.B, D.V.M, N.P.P, J.C.F.P, M.S.M, M.E.T.R were clinical investigators. B.P.M, M.R.G, Y.C.E supervised the trial. B.S.R, L.R.N, R.P.N, T.H.G, T.F.B, M.D.E, J.M.E.P, Y.I.H, I.C.Q, S.F.C, Y.C.R, D.S.M, A.P.D, E.G.O were responsible of immunological evaluations. R.G.M performed the data curation. C.V.S performed statistical analysis. D.G.R, C.V.S, Y.G.V, Y.V.B and V.V.B wrote the manuscript. The members of SOBERANA Research Group participated in different processes during the trial: data collection, supervision, quality assurance, coordination among others.

Declaration of competing interest

The authors RPG, YRD, CRI, LCH, MPB, DVM, NPP, CVS, APD, EGO, YCE, JCFP, MSM, MDE, JMPEP, YIH, and METR declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors BPM, MRG, BSR, LMRN, RPN, RGM, THG, TFB, ICQ, SFC, YCR, DSM, YGV, YVB, DGR, and VVB work at Finlay Vaccine Institute or the Centre of Molecular Immunology, institutions that develop and manufacture the vaccine candidates but have not received an honorarium for this paper.

BSR, SFC, YCR, LRN, DSM, YVB, DGR, and VVB have filed patent applications related to the vaccine FINLAY-FR-2.

DD and AB work at Pasteur Institute of Iran and are co-developer of the vaccines.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.016.

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