HUMAN VACCINES & IMMUNOTHERAPEUTICS
2024, VOL. 20, NO. 1, 2425147
https://doi.org/10.1080/21645515.2024.2425147

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Immunogenicity and safety following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine with Matrix-M™ adjuvant (NVX-CoV2373) versus a primary series in people living with and without HIV-1 infection in South Africa: A randomized crossover phase 2a/2b trial

Vivek Shinde[a], Anthonet Lombard Koen[b], Zaheer Hoosain[c], Moherndran Archary[d], Qasim Bhorat[e], Lee Fairlie[f], Umesh Lalloo[g], Mduduzi S. L. Masilela[h], Dhayendre Moodley[i], Sherika Hanley[j], Leon Frederik Fouche[k], Cheryl Louw[l,m], Michele Tameris[n], Nishanta Singh[o], Ameena Goga[o], Keertan Dheda[p], Coert Grobbelaar[q], Natasha Joseph[r], Johan J. Lombaard[c], Rosie Mngqibisa[d], As'ad Ebrahim Bhorat[e], Gabriella Benadé[f], Natasha Lalloo[g], Anna Pitsi[h], Pieter-Louis Vollgraaff[k], Angelique Luabeya[n], Aliasgar Esmail[p], Friedrich G. Petrick[s], Aylin Oommen Jose[b], Sharne Foulkes[c], Khatija Ahmed[h,t], Asha Thombrayil[b], Dishiki Kalonji[b,o], Shane Cloney-Clark[a], Mingzhu Zhu[a], Chijioke Bennett[a], Gary Albert[a], Alex Marcheschi[a], Joyce S. Plested[a], Susan Neal[a], Gordon Chau[a], Iksung Cho[a], Louis Fries[a], Greg M. Glenn[a], Shabir A. Madhi[b], and for the 2019nCoV-501 Study Group

[a]Research and Development, Novavax, Inc, Gaithersburg, MD, USA; [b]South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [c]Research and Development, Josha Research Centre, Bloemfontein, Free State, South Africa; [d]Paediatric Infectious Diseases Unit, University of KwaZulu-Natal, Durban, South Africa; [e]Research and Development, Soweto Clinical Trials Centre, Johannesburg, South Africa; [f]Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [g]Respiratory and Critical Care Unit, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa; [h]Research and Development, Setshaba Research Centre, Tshwane, South Africa; [i]Department of Obstetrics and Gynaecology, University of KwaZulu-Natal, Durban, South Africa; [j]Centre for the AIDS Programme of Research in South Africa (CAPRISA), and Department of Family Medicine, University of KwaZulu-Natal, Durban, South Africa; [k]Research and Development, Limpopo Clinical Research Initiative, Thabazimbi, South Africa; [l]Research and Development, Madibeng Centre for Research, Brits, South Africa; [m]Faculty of Health Sciences, Department of Family Medicine, University of Pretoria, Pretoria, South Africa; [n]South African TB Vaccine Initiative, University of Cape Town, Cape Town, South Africa; [o]South African Medical Research Council, HIV and other Infectious Diseases Research Unit (HIDRU) and, Health Systems Research Unit, Durban, South Africa; [p]Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute, University of Cape Town, Cape Town, South Africa; [q]Aurum Institute, University of Pretoria, Pretoria, South Africa; [r]Research and Development, PEERMED Clinical Trial Centre, Kempton Park, South Africa; [s]Research and Development, MERC Research, Middelburg, South Africa; [t]Faculty of Health Sciences, Department of Microbiology, University of Pretoria, Pretoria, South Africa

ABSTRACT

COVID-19 remains a global public health issue and an improved understanding of vaccine performance in immunocompromised individuals, including people living with HIV (PLWH), is needed. Initial data from the present study's pre-crossover/booster phase were previously reported. This phase 2a/b clinical trial in South Africa (2019nCoV-501/NCT04533399) revisits 1:1 randomly assigned HIV-negative adults (18–84 years) and medically stable PLWH (18–64 years) who previously received two NVX-CoV2373 doses (5 µg recombinant Spike protein with 50 µg Matrix-M™ adjuvant) or placebo. During the 6-month blinded crossover/booster phase, NVX-CoV2373 recipients could receive a single NVX-CoV2373 booster dose and placebo recipients a 2-dose NVX-CoV2373 primary series. NVX-CoV2373 safety and immunogenicity were assessed according to prior SARS-CoV-2 infection and HIV status. Post-crossover, 1900/3793 NVX-CoV2373 recipients were assigned another dose, and 1893/3793 placebo recipients were assigned NVX-CoV2373 primary series. Approximately 56% of the participants were SARS-CoV-2–seropositive ("seropositive") at crossover (6% PLWH). In seropositive participants (HIV-negative and PLWH), booster-dose anti-spike IgG, MN_{50} and hACE2 inhibition responses increased to similar levels, exceeding those in seronegative participants. In primary-series and booster cohorts, seronegative PLWH showed higher neutralizing responses (4.9- to 5.5-fold, respectively) versus peak pre-crossover primary-series responses. The safety profile was similar among the pre-crossover/booster phase groups; solicited and unsolicited adverse events were infrequent in all groups. A single NVX-CoV2373 booster dose substantially increased antibodies. All baseline seropositive participants showed higher immune responses than seronegative participants. These findings support use of NVX-CoV2373, including in immunocompromised individuals.

ARTICLE HISTORY
Received 28 June 2024
Revised 24 October 2024
Accepted 31 October 2024

KEYWORDS
Novavax, Inc.; the Bill & Melinda Gates Foundation; and the Coalition for Epidemic Preparedness Innovations

CONTACT Vivek Shinde vshinde@novavax.com Novavax, Inc, 700 Quince Orchard Road, Gaithersburg, MD 20878, USA.
Supplemental data for this article can be accessed on the publisher's website at https://doi.org/10.1080/21645515.2024.2425147

Introduction

In response to the coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), multiple COVID-19 vaccines have been developed using various technologies to confer immunity against SARS-CoV-2 by targeting the Spike (S) protein or the whole virus.[1,2] Multiple SARS-CoV-2 variants have emerged that are either more transmissible or relatively evasive to neutralizing antibodies (NAbs) induced by infection or COVID-19 vaccines.[1–4] Although primary vaccination series are highly effective in preventing severe disease and death due to COVID-19, there is evidence that NAbs wane substantially over 4 to 6 months.[1,5–8] Consequently, vaccine-induced protection against mild-to-moderate COVID-19 wanes over time. The use of homologous/heterologous booster strategies may bolster waning antibody-mediated immunity and increase protection against emerging SARS-CoV-2 variants.[1,9–15]

Novavax has developed a SARS-CoV-2 recombinant S protein nanoparticle vaccine (SARS-CoV-2 rS) co-formulated with a saponin-based adjuvant, Matrix-M™ (NVX-CoV2373). Overall vaccine efficacy of 89.7% and 90.4% in the United Kingdom (UK) and the United States (US), respectively, was reported for NVX-CoV2373 in phase 3 trials, including 100% efficacy against moderate and severe disease in the US study.[16,17] NVX-CoV2373 has received emergency use/conditional authorization in numerous geographies as a primary series and/or booster and has been deployed globally.

The present study is a phase 2a/b clinical trial of NVX-CoV2373 in South Africa (2019nCoV-501/NCT04533399). Early efficacy and immunogenicity results from this trial demonstrated intermediate vaccine efficacy (49.4% overall, 60.1% among human immunodeficiency virus [HIV]–negative participants) in the context of predominant circulation of the relatively NAb-evasive Beta variant. Here, we revisit these same participants after a 6-month crossover, where NVX-CoV2373 recipients were given a single NVXCoV2373 booster dose and placebo recipients were given a 2-dose NVX-CoV2373 primary series. This analysis assessed safety and immunogenicity of a booster dose versus primary series according to prior SARS-CoV-2 exposure and HIV status.

Methods

Trial design and participants

The detailed study methods have been previously described, and the trial protocol is available online (version 6.0);[18,19] further details are in the Supplemental Methods. Briefly, this is a follow-up immunogenicity and safety analysis of the crossover/booster phase of a randomized, observer-blinded, placebo-controlled phase 2a/b trial. Two doses of NVX-CoV2373 or placebo were administered 21 days apart, with a blinded crossover/booster after 6 months where initial placebo recipients received a primary series and initial primary series recipients received a booster dose. All participants provided written informed consent, and the study was approved by relevant ethics committees.

Eligible participants were adults aged 18–84 years without HIV-1, or people living with HIV (PLWH) aged 18–64 years; medically stable PLWH were included (see Supplemental Methods). Enrolled participants were required to have a non-reactive nucleic acid amplification test (NAAT) for SARS-CoV-2 within 5 days prior to first study vaccination (Day 0). Baseline SARS-CoV-2–naïve (called "baseline seronegative") was defined as the absence of serum anti-S immunoglobulin G (IgG) antibodies (based on sensitivity of 94.7% and a specificity of 96.4% at a predefined anti-S IgG threshold) on Day 0 and no reactive SARS-CoV-2 NAAT during the 14 days after the second vaccination (ie, up to Day 35). Baseline SARS-CoV-2–exposed (called "baseline seropositive") was defined by the presence of serum anti-S IgG at day 0 or reactive SARS-CoV-2 NAAT during the 14 days after the second vaccination.

As some participants became seropositive during the initial pre-crossover phase, serostatus was reassessed at Day 201 (crossover serostatus), with "Day 201–seronegative" indicating participants who met both of the following criteria: 1) anti-nucleocapsid (N)–negative through the first 3 months, and 2) SARS-CoV-2 NAAT–negative through Day 201; "Day 201–seropositive" were participants positive for either of these criteria.

Randomization and masking

Participants were initially randomized 1:1 to receive two intramuscular injections of NVX-CoV2373 or placebo, 21 days apart. Approximately 6 months later, participants underwent a blinded crossover/booster. Participants received two injections 21 days apart (on Days 201 and 222): two doses of NVX-CoV2373 for initial placebo recipients, or one booster dose of NVX-CoV2373 and one dose of placebo for initial NVX-CoV2373 recipients. Unblinded study personnel prepared and administered injections only; all other staff and participants remained blinded to study-group assignment.

Study objectives

The objectives during the crossover/booster period were: a) to describe the immune response to NVX-CoV2373 primary 2-dose regimen plus booster vaccination (by anti-S IgG, NAbs against wild-type SARS-CoV-2, and human angiotensin-converting enzyme 2 (hACE2) inhibition antibody responses) in healthy HIV-negative participants and medically stable PLWH, and stratified by baseline SARS-CoV-2 serostatus; and b) to assess safety by evaluating all unsolicited adverse events (AEs) through Day 236 (i.e., 35 days after the first crossover/booster vaccination) and any AEs of special interest (AESIs), serious AEs (SAEs), or related medically attended AEs (MAAEs). AESIs included potentially immune-mediated medical conditions and AEs specific to COVID-19 (Table S1) through the end of study. Immunogenicity and safety results through Day 236 are reported here.

Procedures

Participants were enrolled from 17 August 2020 through 25 November 2020 at 16 sites in South Africa. Baseline anti-S IgG antibodies were measured at study entry to determine baseline SARS-CoV-2 serostatus. Blood samples for immunogenicity assessments were collected before vaccination (Day 0), immediately prior to second vaccination (Day 21), 14 days after the second vaccination (Day 35), at 3 and 6 months after the second vaccination, and at 2 weeks following post-crossover/booster vaccination (Day 236). Immune responses were assessed by serum anti-S IgG antibodies, wild-type SARS-CoV-2 NAb activity (microneutralization assay at an inhibitory concentration >50% [MN_{50}]), and hACE2 receptor-binding inhibition (RBI) antibodies, as previously described.[18]

Statistical analyses

The safety analysis set included all participants who received at least one dose of study drug, analyzed according to treatment received. Numbers and percentages (with 95% CI) of participants with MAAEs, AESIs, or SAEs were analyzed for HIV-negative participants and PLWH, and were stratified by baseline SARS-CoV-2 serostatus.

The per-protocol immunogenicity (PP-IMM) analysis set included participants who received both doses of study drug as randomized, were negative for the hepatitis B/hepatitis C virus at study entry, had at least a baseline and one post-treatment serum sample result available after vaccination, and had no major protocol violations that could impact immunogenicity response at the corresponding study visit as assessed by the sponsor prior to unblinding. For each visit, the SARS-CoV-2–unexposed population excluded any illness episode with positive SARS-CoV-2 by any validated NAAT and/or antibody test, if available, prior to each visit. Analysis was also performed to assess if immune responses differed between SARS-CoV-2–naïve and –exposed individuals, and to determine whether prior SARS-CoV-2 exposure alters dosing regimen considerations in a pandemic response. The immunogenicity analyses were also performed using the full analysis set population.

For anti-S IgG, hACE2, and MN_{50}, the geometric mean at each study visit and the geometric mean fold rise (GMFR) compared to baseline (Day 0) or beginning of crossover/booster (Day 201) were summarized by study vaccine group. Immunogenicity values reported below the lower limit of quantification were replaced with 0.5× the lower limit of quantification. Missing values were not imputed.

Role of the funding source

Novavax, Inc. sponsored the study and had primary responsibility for study design, protocol development, study monitoring, data management, and statistical analyses. The Bill & Melinda Gates Foundation provided partial financial support. Investigational vaccine manufacturing support was provided by the Coalition for Epidemic Preparedness Innovations.

Results

A total of 3791 participants remained in the study at the time of the 6-month (Day 201) blinded crossover/booster: 1896 from the initial active cohort (initially vaccinated with a 2-dose primary series of NVX-CoV2373) were assigned to receive a single booster dose of NVX-CoV2373 on Day 201 and a placebo dose on Day 222 (to maintain the blind) and 1895 from the initial placebo cohort were assigned to receive a 2-dose primary series of NVX-CoV2373, 21 days apart, on Days 201/222. Overall, this included 120 participants from the initial active cohort and 113 participants from the initial placebo cohort who were medically stable PLWH.

Demographics

Demographic and baseline characteristics were well balanced between the initial active and placebo cohorts, overall and by HIV status.

Of 4408 participants in the full safety population, 4163 (94.4%) were HIV-negative. This cohort had a median age of 27.0 years (IQR: 23–36) and 4.4% were 65 years of age and older. Most HIV-negative participants were male (2455/4163 [59.0%]) and Black (3953/4163 [95.0%]). Median baseline body mass index (BMI) was 23.30 kg/m^2; 19.2% of participants had a BMI >30 kg/m^2, and 22.3% of participants had any comorbid condition. At baseline, 65.8% of HIV-negative participants were baseline seronegative.

For PLWH, the median age was 38.0 years (IQR: −31 to 46 years). Of 245 PLWH, most (73.1%) were female and 100% were Black. Median baseline BMI was 26.60 kg/m^2; 33.1% had a BMI >30 kg/m^2. Hypertension and diabetes were reported in 6.9% and 1.6% of PLWH, respectively, and 36.3% of participants had any comorbid condition. A negative baseline hepatitis B and hepatitis C status was reported, respectively, for 93.1% and 99.2% of PLWH. Median baseline CD4 level was 741.0 cells/μL (IQR: 539–943) and median baseline HIV viral load was 63.0 copies/mL (IQR: 30–131). At baseline, 65.7% of PLWH were baseline seronegative (Table 1, Figure 1).

Immunogenicity

Post-crossover/booster immunogenicity assessment was affected by high rates of SARS-CoV-2 seropositivity due to prior infection, as 930/1801 (51.6%) participants from the active cohort and 1095/1809 (60.5%) participants from the placebo cohort were either seropositive at baseline (study start) or became seropositive during the pre-crossover/booster phase of the study between Day 0 and Day 201 (300 from the active cohort and 410 in the placebo cohort). To account for this, serostatus was reset at Day 201 (crossover/booster serostatus), with "Day 201–seronegative" indicating participants who were both anti-N–negative through the first 3 months, and SARS-CoV-2 NAAT–negative through Day 201; "Day 201–seropositive" were participants positive for either of these criteria.

Although all crossover/booster participants were administered randomized treatments, blood samples for post-crossover/booster immunogenicity assessment on Day 236 (14

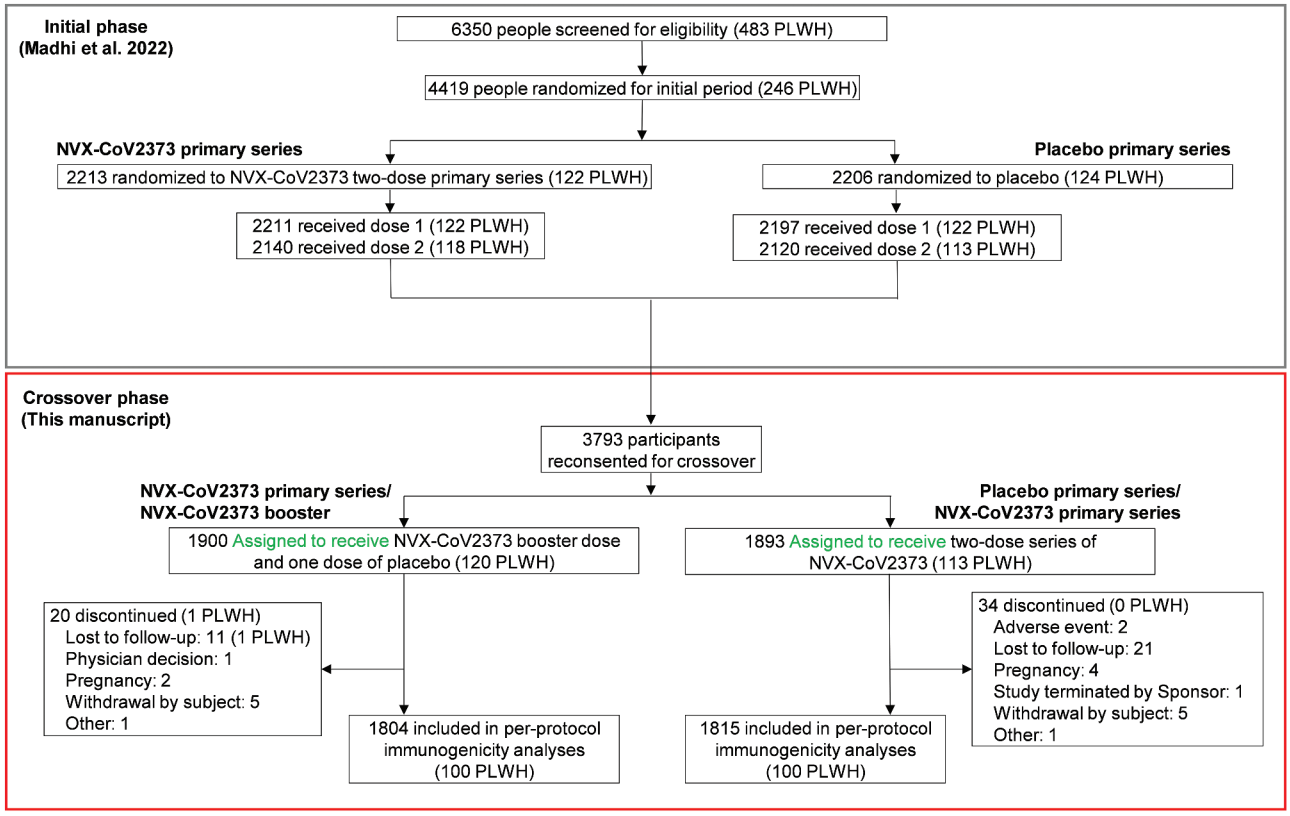

Figure 1. CONSORT diagram. Abbreviations: PLWH, people living with HIV.

days following second vaccination in those receiving primary series during the crossover, and 35 days following booster vaccination in those receiving a single booster dose) were collected from an immunogenicity subset of 3610 participants. In SARS-CoV-2 baseline seronegative, active-cohort participants, expected declines in serum anti-S IgG concentrations were observed following the primary series (Day 35) over a 6-month period until the time of the Day 201 booster (30,593.8 EU/mL to 3610.2 EU/mL; Table S2; Figure S1). Thirty-five days after the booster dose was administered (Day 236), anti-S IgG concentrations in Day 201–seronegative participants increased substantially to 109,311.0 EU/mL compared with a pre-boost concentration of 3050.9 EU/mL (geometric mean fold rise [GMFR]: 31.9). Boosted Day 201–seronegative HIV-negative participants saw a GMFR of 32.1 from 3136.6 EU/mL pre-boost to 114,155.6 EU/mL following the boost. Post-boost values in this HIV-negative group were 3.6-times higher than those at the corresponding Day 35 IgG concentrations observed after primary vaccination (31,738.2 EU/mL). Day 201–seronegative HIV-negative participants from the placebo cohort who received their primary series post-crossover/booster reached anti-S IgG concentrations of 58,973.0 EU/mL at Day 236, which was substantially higher than the 37,738.2 EU/mL response achieved by the baseline seronegative/HIV-negative group receiving their initial primary series during the pre-crossover/booster period.

Of the 200 PLWH in the immunogenicity subset, 40 participants from the active cohort and 23 participants from the placebo cohort remained SARS-CoV-2–seronegative at the time of the crossover/booster (Day 201–seronegative; Table 1). In this subset, boosted participants had GMEUs increase from 1710.9 EU/mL pre-boost to 51,768.6 EU/mL post-boost (GMFR: 29.4), which was higher than the prior peak observed on Day 35 (15,756.9 EU/mL; Table S2; Figure S1).

Day 201–seronegative PLWH from the placebo cohort who received their primary series post-crossover reached an anti-S IgG concentration of 57,006.6 EU/mL, which was essentially comparable to their Day 201–seronegative HIV-negative counterparts (58,973.0 EU/mL), but were notably higher than Day 35 values in baseline seronegative PLWH who received their primary series during the initial pre-crossover period (post-crossover PLWH 57,006.6 EU/mL *vs* initial pre-crossover PLWH 15,756.9 EU/mL; Table S2; Figure S1). In addition, the finding of similar concentrations between Day 201–seronegative PLWH who received two versus three total doses of active vaccine by Day 236 was unique to Day 201–seronegative PLWH, and this pattern was consistent for titers of NAbs to wild-type SARS-CoV-2 (1773.7 *vs* 1584.3; Table 2; Figure 2) and hACE2 RBI antibodies (166.20 EU/mL *vs* 153.68 EU/mL; Table S3; Figure S2).

Overall, neutralization and hACE2 RBI measures showed similar patterns to anti-S IgG. Declines for both titers in SARS-CoV-2 baseline seronegative HIV-negative, active-cohort participants were observed from the time of the primary series up until the time of the crossover/booster for MN_{50} (720.1 to 70.3; Table 2, Figure 2) and hACE2 RBI (86.6 EU/mL to 9.6 EU/mL; Table S3; Figure S2). Two weeks after crossover/booster treatments were administered (Day 236), titers increased robustly

Table 1. Demographics and baseline characteristics – (safety analysis set).

	All Participants			HIV-Negative Participants			PLWH		
Parameter	NVX-CoV2373 N = 2211	Placebo N = 2197	Total N = 4408	NVX-CoV2373 N = 2089	Placebo N = 2074	Total N = 4163	NVX-CoV2373 N = 122	Placebo N = 123	Total N = 245
Age (years)									
Mean (SD)	31.9 (12.9)	32.1 (13.1)	32.0 (13.0)	31.5 (12.9)	31.8 (13.2)	31.6 (13.1)	39.0 (9.9)	38.2 (9.2)	38.6 (9.6)
Median	28.0	28.0	28.0	27.0	27.0	27.0	38.0	38.0	38.0
Min, Max	18, 84	18, 83	18, 84	18, 84	18, 83	18, 84	20, 60	20, 59	20, 60
Age group									
18 to 64 years	2119 (95.8)	2104 (95.8)	4223 (95.8)	1997 (95.6)	1981 (95.5)	3978 (95.6)	122 (100)	123 (100)	245 (100)
65 to 84 years	92 (4.2)	93 (4.2)	185 (4.2)	92 (4.4)	93 (4.5)	185 (4.4)	0	0	0
Sex									
Male	1253 (56.7)	1268 (57.7)	2521 (57.2)	1216 (58.2)	1239 (59.7)	2455 (59.0)	37 (30.3)	29 (23.6)	66 (26.9)
Female	958 (43.3)	929 (42.3)	1887 (42.8)	873 (41.8)	835 (40.3)	1708 (41.0)	85 (69.7)	94 (76.4)	179 (73.1)
Race									
White	88 (4.0)	66 (3.0)	154 (3.5)	87 (4.2)	65 (3.1)	152 (3.7)	1 (0.8)	1 (0.8)	2 (0.8)
Black or African American	2109 (95.4)	2089 (95.1)	4198 (95.2)	1987 (95.1)	1966 (94.8)	3953 (95.0)	122 (100)	123 (100)	245 (100)
Asian	28 (1.3)	27 (1.2)	55 (1.2)	28 (1.3)	27 (1.3)	55 (1.3)	0	0	0
American Indian or Alaska Native	2 (<0.1)	0	2 (<0.1)	2 (<0.1)	0	2 (<0.1)	0	0	0
Native Hawaiian or Other Pacific Islander	2 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)	1 (<0.1)	3 (<0.1)	0	0	0
Other	40 (1.8)	50 (2.3)	90 (2.0)	40 (1.9)	50 (2.4)	90 (2.2)	0	0	0
Multiple	58 (2.6)	38 (1.7)	96 (2.2)	57 (2.7)	37 (1.8)	94 (2.3)	1 (0.8)	1 (0.8)	2 (0.8)
Not Reported	0	2 (<0.1)	2 (<0.1)	0	2 (<0.1)	2 (<0.1)	0	0	0
Ethnicity									
Hispanic or Latino	37 (1.7)	35 (1.6)	72 (1.6)	33 (1.6)	28 (1.4)	61 (1.5)	4 (3.3)	7 (5.7)	11 (4.5)
Not Hispanic or Latino	2172 (98.2)	2160 (98.3)	4332 (98.3)	2054 (98.3)	2044 (98.6)	4098 (98.4)	118 (96.7)	116 (94.3)	234 (95.5)
Not Reported	2 (<0.1)	2 (<0.1)	4 (<0.1)	2 (<0.1)	2 (<0.1)	4 (<0.1)	0	0	0
Baseline BMI (kg/m^2)									
Mean (SD)	25.01 (5.8)	25.00 (5.9)	25.01 (5.8)	24.88 (5.7)	24.85 (5.9)	24.87 (5.8)	27.32 (6.2)	27.53 (5.9)	27.43 (6.1)
Median	23.50	23.50	23.50	23.30	23.30	23.30	26.50	26.60	26.60
Min, Max	12.4, 40.5	16.6, 91.3	12.4, 91.3	12.4, 40.5	16.6, 91.3	12.4, 91.3	17.0, 40.4	18.2, 41.9	17.0, 41.9
Baseline BMI group (kg/m^2)									
30 or lower	1766 (79.9)	1763 (80.2)	3529 (80.1)	1684 (80.6)	1681 (81.8)	3365 (80.8)	82 (67.2)	82 (66.7)	164 (66.9)
Over 30	445 (20.1)	434 (19.8)	879 (19.9)	405 (19.4)	393 (18.9)	798 (19.2)	40 (32.8)	41 (33.3)	81 (33.1)
Participants with medical history reported for									
Hypertension	137 (6.2)	131 (6.0)	268 (6.1)	129 (6.2)	122 (5.9)	251 (6.0)	8 (6.6)	9 (7.3)	17 (6.9)
Diabetes	35 (1.6)	41 (1.9)	76 (1.7)	35 (1.7)	37 (1.8)	72 (1.7)	0	4 (3.3)	4 (1.6)
Participants with no medical history reported	1533 (69.3)	1525 (69.4)	3058 (69.4)	1529 (73.2)	1522 (73.4)	3051 (73.3)	4 (3.3)	3 (2.4)	7 (2.9)
Baseline hepatitis B status									
Negative	2173 (98.3)	2178 (99.1)	4351 (98.7)	2063 (98.8)	2060 (99.3)	4123 (99.0)	110 (90.2)	118 (95.9)	228 (93.1)
Positive	38 (1.7)	19 (0.9)	57 (1.3)	26 (1.2)	14 (0.7)	40 (1.0)	12 (9.8)	5 (4.1)	17 (6.9)
Baseline hepatitis C status									
Negative	2196 (99.3)	2177 (99.1)	4373 (99.2)	2076 (99.4)	2054 (99.0)	4130 (99.2)	120 (98.4)	123 (100)	243 (99.2)
Positive	14 (0.6)	20 (0.9)	34 (0.8)	12 (0.6)	20 (1.0)	32 (0.8)	2 (1.6)	0	2 (0.8)
Missing, n	1	0	1	1	0	1	0	0	0
Comorbidity status									
Yes	519 (23.5)	499 (22.7)	1018 (23.1)	474 (22.7)	455 (21.9)	929 (22.3)	45 (36.9)	44 (35.8)	89 (36.3)
No	1692 (76.5)	1698 (77.3)	3390 (76.9)	1615 (77.3)	1619 (78.1)	3234 (77.7)	77 (63.1)	79 (64.2)	156 (63.7)
Baseline CD4 (cells/μL)									
N	124	124	248	n/a	n/a	n/a	122	123	245
Mean (SD)	764.7 (315.83)	773.4 (307.44)	769.0 (311.06)	n/a	n/a	n/a	760.7 (316.91)	770.9 (307.42)	765.8 (311.58)
Median	737.5	747.0	744.0	n/a	n/a	n/a	729.5	747.0	741.0
Min, Max	80, 2076	182, 1799	80, 2076	n/a	n/a	n/a	80, 2076	182, 1799	80, 2076
Baseline HIV viral load (copies/mL)									
N	39	36	75	n/a	n/a	n/a	39	36	75
Mean (SD)	132.0 (167.38)	110.4 (129.45)	121.7 (149.77)	n/a	n/a	n/a	132.0 (167.38)	110.4 (129.45)	121.7 (149.77)
Median	63.0	62.0	63.0	n/a	n/a	n/a	63.0	62.0	63.0
Min, Max	20, 735	20, 628	20, 735	n/a	n/a	n/a	20, 735	20, 628	20, 735
Day 0 PCR									
Positive	63 (2.8)	63 (2.9)	126 (2.9)	59 (2.8)	60 (2.9)	119 (2.9)	4 (3.3)	3 (2.4)	7 (2.9)
Negative	2148 (97.2)	2134 (97.1)	4282 (97.1)	2030 (97.2)	2014 (97.1)	4044 (97.1)	118 (96.7)	120 (97.6)	238 (97.1)
Day 0 SARS-CoV-2 serostatus									
Positive	660 (29.9)	683 (31.1)	1343 (30.5)	619 (29.6)	643 (31.0)	1262 (30.3)	41 (33.6)	40 (32.5)	81 (33.1)
Negative	1533 (69.3)	1484 (67.5)	3017 (68.4)	1453 (69.6)	1403 (67.6)	2856 (68.6)	80 (65.6)	81 (65.9)	161 (65.7)

(*Continued*)

Table 1. (Continued).

Parameter	All Participants			HIV-Negative Participants			PLWH		
	NVX-CoV2373 N = 2211	Placebo N = 2197	Total N = 4408	NVX-CoV2373 N = 2089	Placebo N = 2074	Total N = 4163	NVX-CoV2373 N = 122	Placebo N = 123	Total N = 245
Indeterminate	18 (0.8)	30 (1.4)	48 (1.1)	17 (0.8)	28 (1.4)	45 (1.1)	1 (0.8)	2 (1.6)	3 (1.3)
Baseline serostatus									
Positive	736 (33.3)	771 (35.1)	1507 (34.2)	693 (33.2)	730 (35.2)	1423 (34.2)	43 (35.2)	41 (33.3)	84 (34.3)
Negative	1475 (66.7)	1426 (64.9)	2901 (65.8)	1396 (66.8)	1344 (64.8)	2740 (65.8)	79 (64.8)	82 (66.7)	161 (65.7)
Day 201 SARS-CoV-2 serostatus (post-crossover safety analysis set)									
Positive	632/1900 (33.3)	659/1893 (34.8)	1291/3793 (34.0)	590/1780 (33.1)	620/1780 (34.8)	1210/3560 (34.0)	42/120 (35.0)	39/113 (34.5)	81/233 (34.8)
Negative	1268/1900 (66.7)	1234/1893 (65.2)	2502/3793 (66.0)	1190/1780 (66.9)	1160/1780 (65.2)	2350/3560 (66.0)	78/120 (65.0)	74/113 (65.5)	152/233 (65.2)
Day 201 SARS-CoV-2 serostatus (from the post-crossover PP-IMM analysis set)									
Day 201–seropositive	930/1801 (51.6)	1095/1809 (60.5)	2025/3610 (56.1)	869/1700 (51.1)	1019/1710 (59.6)	1888/3410 (55.4)	61/101 (60.4)	76/99 (76.8)	137/200 (68.5)
Day 201–seronegative	871/1801 (48.4)	714/1809 (39.5)	1585/3610 (43.9)	831/1700 (48.9)	691/1710 (40.4)	1522/3410 (44.6)	40/101 (39.6)	23/99 (23.2)	63/200 (31.5)

Abbreviations: BMI = body mass index; ELISA = enzyme-linked immunosorbent assay; GMEU = geometric mean ELISA unit; HIV = human immunodeficiency virus; IgG = immunoglobulin G; Max = maximum; Min = minimum; n/a = not applicable; NAAT = nucleic acid amplification test; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PCR = polymerase chain reaction; PLWH, people living with HIV; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation.

Day 0 PCR positive was defined as (+) PCR (NAAT) on Day 0 swab. Day 0 SARS-CoV-2 serostatus positive was defined as anti-S IgG antibody level detected by ELISA using GMEUs on Day 0 serology. Baseline serostatus positive was defined by anti-S IgG antibody level detected by ELISA using GMEUs on Day 0 serology and/or (+) PCR (NAAT) detected between Day 0 through Day 21.

Data are presented as number and percentage (n [%]) of participants unless stated otherwise.

The safety analysis set included all participants who received at least one dose of study drug, analyzed according to treatment received. For the post-crossover PP-IMM analysis sets, "Day 201–seronegative" includes participants who were both anti-N–negative through the first 3 months, and SARS-CoV-2 NAAT–negative through Day 201; "Day 201–seropositive" participants were positive for either one of the aforementioned criteria.

compared to both the pre-boost and Day 35 titers recorded after the primary series. In boosted Day 201–seronegative HIV-negative participants, from Day 201 to Day 236, GMFR for MN_{50} titers was ~58.3, increasing from 56.7 to 3876.5 (Table 2); and hACE2 RBI titers increased from 7.76 EU/mL to 379.07 EU/mL (GMFR: 45.8; Table S3), for pre- to post-boost. Post-boost titers were higher than Day 35 titers after the initial primary series (MN_{50}: 5.4-times higher; hACE2 RBI: 4.4-times higher).

Day 201–seronegative HIV-negative participants from the placebo cohort who received their primary series post-crossover reached MN_{50} titers of 1432.8 and hACE2 RBI titers of 210.57 EU/mL, which were substantially higher than the corresponding baseline seronegative HIV-negative participants who received their primary series during the initial pre-crossover period.

In boosted Day 201–seronegative PLWH, robust increases in MN_{50} (Table 2; Figure 2) and hACE2 RBI (Table S3; Figure S2) titers were observed, much like anti-S IgG concentrations, but again responses were reduced when compared with HIV-negative participants. However, when examining responses seen in boosted, Day 201–seropositive PLWH, this gap in immunogenicity titers was generally eliminated *vs* Day 201–seropositive HIV-negative participants (Day 236: IgG, 121,481.7 EU/mL *vs* 118,947.7 EU/mL; $MN_{50,}$ 3683.7 *vs* 3744.6; and hACE2 RBI, 399.87 EU/mL *vs* 359.07 EU/mL).

Antibody titers were notably different in participants who were Day 201–seropositive compared with Day 201–seronegative individuals at different time points throughout the study. In HIV-negative baseline seropositive participants, anti-S IgG concentrations (1751.9 EU/mL) were initially ~16-times higher than their baseline seronegative counterparts (111.4 EU/mL) at Day 0 (Table S2). Two weeks following primary vaccination, respective values (101,617.3 EU/mL *vs* 31,738.2 EU/mL) were ~3.2-times higher in the HIV-negative, baseline seropositive versus seronegative populations. Day 0 responses in baseline seropositive versus seronegative PLWH were 1852.9 EU/mL *vs* 118.4 EU/mL and had less of a difference two weeks following primary vaccination at Day 35 (98,399.5 EU/mL *vs* 15,756.9 EU/mL). These Day 35 anti-S IgG concentrations in baseline seropositive HIV-negative participants were comparable to those seen in Day 201–seronegative, boosted HIV-negative participants (following three doses of vaccine) at Day 236 (101,617.3 EU/mL *vs* 114,155.6 EU/mL), but higher than in corresponding PLWH cohorts (98,399.5 EU/mL *vs* 51,768.6 EU/mL).

By Day 201 (approximately 6 months after the second dose of the initial primary series on Day 21), anti-S IgG concentrations in both the Day 201–seropositive (11,205.5 EU/mL) and Day 201–seronegative (3136.6 EU/mL) HIV-negative cohorts (again, serostatus was reestablished at Day 201) were 9- and 10-times lower than peak levels observed at Day 35 (101,617.3 EU/mL and 31,738.2 EU/mL, respectively; Table S2). Similar patterns of antibody kinetics were seen in corresponding PLWH cohorts. At Day 236, anti-S IgG concentrations were balanced across HIV-negative boosted Day 201–seropositive, primary-vaccinated Day 201–seropositive, and boosted Day 201–seronegative participants (118,947.7 EU/mL, 123,757.4 EU/mL, and 114,155.6 EU/mL, respectively) and notably greater than primary-vaccinated Day

Table 2. Comparison of SARS-CoV-2 wild-type virus microneutralisation in hiv-negative participants and medically stable PLWH stratified by serostatus (per protocol immunogenicity analysis set).

Serum Antibody Parameters	Seronegative[a]			Seropositive[a]			Regardless of Serostatus[a]		
	All Participants	HIV-Negative	PLWH	All Participants	HIV-Negative	PLWH	All Participants	HIV-Negative	PLWH
Baseline Serostatus									
GMT at Day 0 (95% CI)									
n1/n2	1164/1111	1102/1051	62/60	626/682	587/645	39/37	1792/1798	1691/1701	101/97
NVX-CoV2373	10.2 (10.1–10.3)	10.2 (10.0–10.3)	10.5 (10.0–10.9)	58.9 (53.2–65.1)	58.0 (52.3–64.3)	74.5 (48.3–115.0)	18.8 (17.8–19.8)	18.6 (17.6–19.6)	22.3 (17.4–28.7)
Placebo	10.3 (10.1–10.4)	10.3 (10.1–10.4)	10.5 (9.9–11.1)	53.7 (48.8–59.1)	52.8 (47.8–58.3)	72.8 (49.7–106.7)	19.3 (18.3–20.3)	19.1 (18.1–20.2)	21.9 (17.3–27.9)
GMT at Day 35 (95% CI)									
n1/n2	1142/1097	1082/1036	60/61	604/655	565/619	39/36	1748/1756	1649/1659	99/97
NVX-CoV2373	690.4 (640.1–744.8)	720.1 (666.7–777.7)	323.7 (229.6–456.3)	3158.2 (2857.1–3491.1)	3188.7 (2888.3–3520.2)	2748.6 (1478.2–5110.9)	1168.4 (1090.3–1252.2)	1199.8 (1119.0–1286.4)	751.8 (515.3–1096.9)
Placebo	10.8 (10.5–11.1)	10.7 (10.5–11.0)	12.1 (10.7–13.8)	65.2 (58.8–72.4)	65.2 (58.6–72.7)	64.7 (41.5–100.9)	21.2 (20.0–22.5)	21.1 (19.9–22.4)	22.6 (17.7–28.8)
GMFR Day 35:Day 0 (95% CI)									
NVX-CoV2373	67.70 (62.7–73.0)	70.7 (65.4–76.4)	30.9 (22.1–43.3)	52.9 (47.9–58.4)	54.2 (49.2–59.8)	36.9 (20.5–66.4)	62.2 (58.5–66.1)	64.6 (60.8–68.7)	33.1 (24.5–44.9)
Placebo	1.1 (1.0–1.1)	1.0 (1.0–1.1)	1.2 (1.0–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.9 (0.6–1.5)	1.1 (1.1–1.1)	1.1 (1.1–1.1)	1.1 (0.9–1.3)
GMT at Day 111 (95% CI)									
n1/n2	1133/1087	1073/1029	60/58	600/651	563/615	37/36	1735/1743	1638/1649	97/94
NVX-CoV2373	120.4 (111.6–129.8)	121.2 (112.3–130.8)	106.8 (70.0–162.9)	887.5 (792.8–993.5)	881.5 (785.2–989.4)	984.7 (580.1–1671.5)	240.3 (222.5–259.6)	239.8 (221.7–259.3)	249.2 (168.5–368.5)
Placebo	13.2 (12.6–13.8)	12.9 (12.3–13.5)	20.5 (15.7–26.7)	68.0 (61.5–75.1)	67.5 (60.9–74.8)	77.0 (49.3–120.1)	24.4 (23.0–25.9)	23.9 (22.5–25.4)	34.0 (26.0–44.4)
GMFR Day 111:Day 0 (95% CI)									
NVX-CoV2373	11.8 (10.9–12.7)	11.9 (11.0–12.8)	10.2 (6.7–15.4)	14.7 (13.3–16.3)	14.9 (13.4–16.6)	12.1 (7.5–19.3)	12.7 (12.0–13.5)	12.9 (12.1–13.7)	10.9 (8.0–14.8)
Placebo	1.3 (1.2–1.3)	1.2 (1.2–1.3)	2.0 (1.5–2.6)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.1 (0.7–1.7)	1.3 (1.2–1.3)	1.3 (1.2–1.3)	1.6 (1.3–2.0)
GMT at Day 201 (95% CI)									
n1/n2	1113/1075	1054/1015	59/60	600/655	563/618	37/37	1715/1735	1619/1638	96/97
NVX-CoV2373	69.3 (63.3–75.9)	70.3 (64.0–77.2)	53.7 (37.3–77.3)	582.2 (517.0–655.5)	573.6 (507.5–648.2)	729.7 (439.2–1212.2)	146.0 (133.9–159.2)	145.9 (133.5–159.5)	146.7 (99.3–216.7)
Placebo	13.9 (13.2–14.6)	13.6 (12.9–14.4)	18.9 (15.0–23.7)	68.5 (62.0–75.8)	68.2 (61.5–75.7)	74.2 (49.8–110.7)	25.4 (23.9–27.0)	25.1 (23.5–26.7)	31.8 (24.9–40.6)
GMFR Day 201:Day 0 (95% CI)									
NVX-CoV2373	6.8 (6.2–7.4)	6.9 (6.3–7.6)	5.1 (3.6–7.3)	9.8 (8.8–10.9)	9.8 (8.8–11.0)	9.3 (5.9–14.7)	7.7 (7.2–8.3)	7.8 (7.3–8.4)	6.4 (4.9–8.5)
Placebo	1.4 (1.3–1.4)	1.3 (1.3–1.4)	1.8 (1.4–2.2)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.0 (0.7–1.6)	1.3 (1.3–1.4)	1.3 (1.3–1.4)	1.5 (1.2–1.8)
Day 201 Crossover/Booster Serostatus									
GMT at Month 6 (Day 201) (95% CI)									
n1/n2	832/690	793/667	39/23	883/1045	826/971	57/74	1715/1735	1619/1638	96/97
NVX-CoV2373	55.6 (50.6–61.0)	56.7 (51.5–62.4)	37.3 (24.6–56.4)	362.5 (323.3–406.6)	361.7 (321.2–407.3)	374.8 (237.3–592.0)	146.0 (133.9–159.2)	145.9 (133.5–159.5)	146.7 (99.3–216.7)
Placebo	11.3 (10.8–11.8)	11.3 (10.8–11.8)	11.6 (10.0–13.6)	43.3 (39.8–47.1)	43.3 (39.7–47.3)	43.5 (32.9–57.6)	25.4 (23.9–27.0)	25.1 (23.5–26.7)	31.8 (24.9–40.6)
GMT at Day 236 (95% CI)									
n1/n2	306/265	289/252	17/13	379/463	339/417	40/46	685/728	628/669	57/59
NVX-CoV2373 to Booster	3711.7 (3292.1–4184.9)	3876.5 (3430.1–4381.1)	1773.7 (1069.5–2941.4)	3738.1 (3399.4–4110.6)	3744.6 (3394.5–4130.8)	3683.7 (2574.0–5271.8)	3726.3 (3457.5–4016.0)	3804.7 (3522.4–4109.8)	2962.2 (2197.8–3992.4)
Placebo to NVX-CoV2373	1439.9 (1238.0–1674.7)	1432.8 (1229.3–1670.0)	1584.3 (617.3–4066.3)	3981.4 (3611.7–4389.0)	4063.7 (3662.4–4509.1)	3307.4 (2510.5–4357.3)	2749.5 (2512.8–3008.4)	2744.0 (2496.2–3016.5)	2812.3 (2097.4–3770.8)
GMFR Day 236:Day 201 (95% CI)									
NVX-CoV2373 to Booster	57.0 (48.0–67.7)	58.3 (48.8–69.6)	39.2 (18.7–82.5)	9.0 (7.7–10.7)	9.3 (7.8–11.0)	7.5 (4.3–12.9)	20.6 (18.0–23.6)	21.6 (18.7–24.9)	12.(2 7.6–19.7)
Placebo to NVX-CoV2373	128.3 (109.2–150.8)	128.4 (108.8–151.4)	128.0 (53.5–306.1)	82.2 (72.3–93.4)	81.7 (71.2–93.8)	86.5 (62.2–120.3)	96.7 (87.3–107.0)	96.9 (87.0–107.8)	94.3 (69.2–128.6)

ELISA, enzyme-linked immunosorbent assay; GMEU, geometric mean ELISA unit; GMFR, geometric mean fold rise; GMT, geometric mean titer; n1, number of participants in the NVX-CoV2373 group; n2, number of participants in the placebo group; PLWH, people living with HIV.

[a]All participants had a non-reactive nucleic acid amplification test (NAAT) for SARS-CoV-2 within 5 days before receipt of study vaccine at Day 0. Baseline seronegativity was defined by absence of anti-S IgG antibodies on Day 0 and no reactive SARS-CoV-2 NAAT for 14 days after the second vaccine (up to Day 35). At Day 201, serostatus was reassessed because some participants became seropositive during the pre-crossover/booster phase. "Day 201–seronegative participants were those who were both anti-N–negative through the first 3 months, and SARS-CoV-2 NAAT–negative through Day 201; "Day 201–seropositive" participants were positive for either one of the aforementioned criteria.

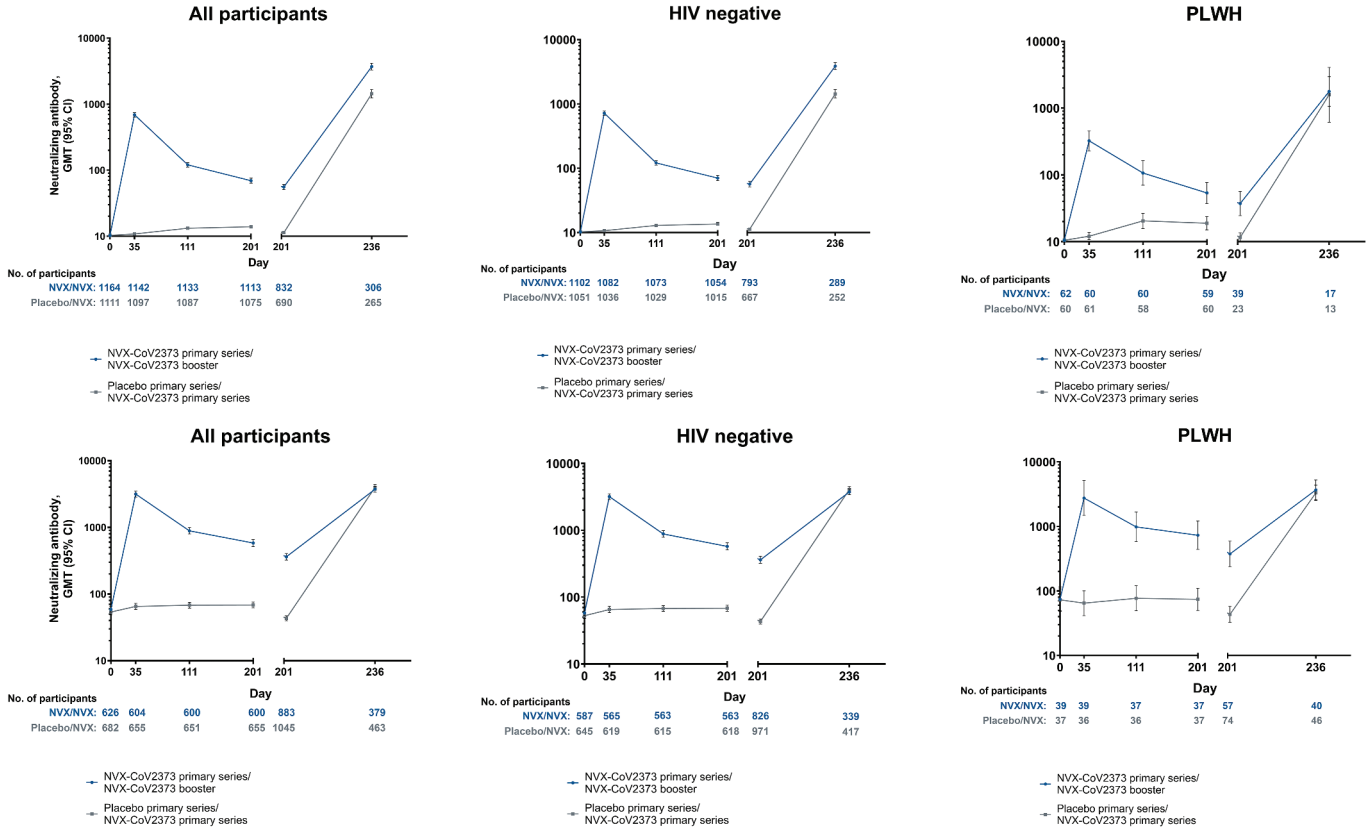

Figure 2. Neutralizing antibody activity to wild-type SARS-CoV-2 by study day (log scale). Levels of NAbs to wild-type SARS-CoV-2 (measured by the microneutralisation assay) were assessed for all participants, hiv-negative participants only, and PLWH only, stratified by SARS-CoV-2 serostatus. GMTs with 95% CI are shown; error bars smaller than the size of the graphed symbol are not visible. Serostatus was assessed at baseline, and points from Day 0 to the first measurement of Day 201 on each graph are based on baseline serostatus. On Day 201, serostatus was reassessed because some participants became seropositive during the pre-crossover phase. Points on each graph from the second instance of Day 201 to Day 236 are based on this reassessed serostatus. The number of participants in each group is shown for each time point below the graphs. Abbreviations: CI, confidence interval; GMT, geometric mean titer; NAbs, neutralizing antibodies; PLWH, people living with HIV.

201–seronegative participants (58,973.7 EU/mL). Among PLWH at Day 236, anti-S IgG concentrations were higher amongst boosted Day 201–seropositive participants, followed by primary-vaccinated Day 201–seropositive participants, and then followed by boosted Day 201–seronegative or primary-vaccinated Day 201–seronegative participants (121,481.7 EU/mL *vs* 83,231.4 EU/mL *vs* 51,768.6 EU/mL *vs* 57,006.6 EU/mL).

The majority of the serostatus-related trends observed with IgG were also observed in NAb activity (Table 2; Figure 2) and hACE2 RBI (Table S3; Figure S2). One exception was that Day 201–seropositive participants (at 6 months) who received their primary vaccination post-crossover attained higher titers at Day 236 than either the boosted Day 201–seropositive or Day 201–seronegative participants for both NAb activity (MN_{50} of 3981.4 *vs* 3738.1 and 3711.7, respectively) and hACE2 RBI (GMT of 424.93 EU/mL *vs* 364.23 EU/mL and 362.31 EU/mL, respectively).

Safety

Post-crossover/booster, all unsolicited AEs were collected between Day 201 and Day 236. Overall, unsolicited AEs in this timeframe had comparable incidence in participants who received a booster (227/1900 [11.9%]) or the primary series (239/1893 [12.6%]; Table S4). Most events were mild or moderate in severity; severe events were reported in 3/1900 (0.2%) participants in the booster group and in 2/1893 (0.1%) participants in the crossover/primary series group. Two participants in the booster group had severe events (injection-site pain, erythema, and/or induration) that were considered related to study vaccination. MAAEs were also reported with a slightly higher frequency in participants receiving a booster (7/1900 [0.4%]) *vs* primary series (2 [0.1%]). No events considered PIMMCs were reported, and AESI related to COVID-19 were balanced between groups (4 [0.2%] participants in each group, reporting events of ageusia and/or anosmia only). SAEs were rare, occurring at a lower frequency in participants receiving the booster (1/1900 [<0.1%]) versus the primary series (4/1893 [0.2%]). The SAE in the booster recipient was renal failure; events in the primary series group were one event each of gunshot wound, pneumonia, rotator-cuff syndrome, and abortion spontaneous. No SAEs were assessed by investigators as related to study vaccine. Post-crossover through Day 236, there was one discontinuation due to an AE. This was one participant in the primary series group who discontinued the study vaccine due to an AE.

Discussion

In this report, we describe the safety and immunogenicity of a booster dose of NVX-CoV2373 in the context of a unique phase 2a/b, randomized, observer-blinded, placebo-controlled study, administered concurrently with another cohort receiving their initial primary series in a population of HIV-negative participants and PLWH, with or without prior SARS-CoV-2 infection. Administration of a single booster dose of the vaccine approximately 6 months following the 2-dose primary series resulted in enhanced immunogenicity versus those only receiving their primary series but maintained a comparable safety profile. However, the specific patterns of booster vaccine-induced immune responses varied depending on SARS-CoV-2 serostatus and HIV status.

As expected, in previously immunized baseline seronegative HIV-negative participants, pre-boost anti-S IgG concentrations at Day 201 (3136.6 EU/mL) had declined substantially from the peak Day 35 concentrations (31,738.2 EU/mL) following the primary series. Antibody responses to a single booster dose were robust, with anti-S IgG, MN_{50}, and hACE2 RBI GMFRs from Day 201 to Day 236 of 32.1, 58.3, and 45.8, respectively; each of these Day 236 responses were also higher than those at Day 35 (after the primary series). Data on the immunogenicity of a homologous boost with NVX-CoV2373 was recently reported for an earlier Phase 2 trial in the US and Australia in Mallory et al.[13] There, and in the present study, anti-S IgG antibody levels in baseline seronegative subjects declined similarly at approximately 6 months post-primary series, as well as increased 3 weeks post-booster dose. Post-booster responses in Mallory et al.[13] were also analyzed using fit-for-purpose assays to assess anti-rS IgG and neutralizing antibody activity against SARS-CoV-2 variants of concern (VOCs), including the Omicron BA.1 subvariant. In that study, over the same time frame, responses following the booster showed approximately 61.1-fold (original Wuhan strain) and approximately 73.4-fold (Omicron BA.1 subvariant) increases in anti-rS IgG antibody activity when compared to the 6-month pre-booster time point. In a separate investigation of pseudovirus NAb responses against Omicron subvariants BA.1 and BA.4/BA.5, a subset of 48 Day 201–seronegative HIV-negative participants from the present study demonstrated a 35- and 12-fold increase, respectively, in post-boost peak (Day 236) antibody responses compared to their post-primary series peak (Day 35) responses. This represented a restoration of neutralizing activity against BA.1 comparable to levels achieved against the vaccine-homologous prototype strain following the primary series.[20] Notably, booster NAb responses against BA.1 and BA.4/BA.5 were similarly high for NVX-CoV2373 and BNT162 (Pfizer-BioNTech) mRNA vaccines, and both were substantially higher than the AD26.COV.2 (Jansen) vaccine in that study,[20] with both of the latter vaccines having demonstrated notable protection against severe disease from Omicron BA.1 even after only the primary series in South Africa.[21]

Among HIV-negative participants, the subset of SARS-CoV-2–seropositive participants showed consistently higher titers than their seronegative counterparts following receipt of NVX-CoV2373 primary series (either during the pre- or post-crossover phases), demonstrating an incremental benefit of hybrid immunity in the context of a primary vaccine series (e.g., anti-S IgG concentrations of 101,617.3 EU/mL in baseline seropositive *vs* 31,738.2 EU/mL in baseline seronegative [during pre-crossover, Day 35]; and 123,757.4 EU/mL in Day 201–seropositive *vs* 58,973.0 EU/mL in Day 201–seronegative [during post-crossover, Day 236], respectively). Like their baseline seronegative counterparts, initial primary series–vaccinated seropositive participants saw a similar proportional decline in antibody titers over 6 months. Following receipt of the booster dose, Day 201–seropositive participant concentrations appeared to "top off" to levels comparable to their prior post-primary series peak response (118,947.7 EU/mL post-boost versus 101,617.3 EU/mL post-primary series) and notably were comparable to responses in boosted Day 201–seronegative participants (114,155.6 EU/mL). The observation that three doses of vaccine in Day 201–seronegative participants elicited a similar antibody response as either two or three doses of vaccine in Day 201–seropositive participants, implies both that a 3-dose series in seronegative participants can match hybrid immunity in seropositive participants, and that once hybrid immunity is established in seropositive participants, there does not appear to be an incremental advantage (i.e., an increase in amplitude of the homologous antibody response) to hybrid immunity in the context of a homologous booster.

For Day 201–seronegative participants receiving their primary series during the crossover, peak Day 236 antibody concentrations (58,973.0 EU/mL) were 1.9-times higher than the corresponding peak Day 35 concentrations from Day 201–seronegative participants vaccinated with the primary series during the initial phase of the study (31,738.2 EU/mL). The higher concentrations in post- versus pre-crossover primary series recipients were achieved using vaccine manufactured by a more advanced, late-stage large-scale production process (as compared to early stage, small-scale material used in the initial phase of the present study) and was similar to the vaccine used in the US Phase 3 efficacy trial of NVX-CoV2373. Notably, the antibody responses to the primary series in the crossover phase of the present study were similar to those observed for the primary series in the US/Mexico Phase 3 efficacy study in which those titers were associated with a vaccine efficacy of approximately 93% against contemporaneously circulating variants of interest (VOI)/VOC (particularly the Alpha variant).[16,22] Vaccine efficacy against the Beta variant (which was predominantly circulating in South Africa during this trial[19] may have been underestimated in the pre-crossover phase due to the use of less fully developed vaccine material. This is likely to have partially accounted for the lower efficacy estimates observed in the initial pre-crossover phase of the present study versus the high efficacy observed in the US/Mexico Phase 3 study.[7,16,19]

We previously reported data from the initial pre-crossover /booster phase of the present study that showed anti-S IgG and NAb responses to NVX-CoV2373 that were reduced 2-fold in baseline seronegative PLWH when compared to baseline seronegative HIV-negative participants following the primary series.[18] However, again, in the post-crossover/booster phase of the present study, with use of later stage vaccine, this

difference was eliminated in participants first vaccinated post-crossover (e.g., IgG concentrations were 57,006.6 EU/mL in Day 201–seronegative PLWH *vs* 58,973.0 EU/mL in Day 201–seronegative HIV-negative participants, at Day 236). This is consistent with the hypothesis that this difference was due to sensitivity of seronegative PLWH to the potency of original vaccine material used in pre-crossover/booster period versus an inherent difference in vaccine-induced immune response related to underlying HIV status. Notably, this difference did not exist between seropositive PLWH and seropositive HIV-negative participants, either with the original material used pre-crossover/booster, or with the later-stage vaccine used in the post-crossover/booster period, suggesting a role for natural priming in overcoming any potency limitations with the original vaccine used in the pre-crossover/booster period. Interestingly, however, boosting with later-stage vaccine on top of a primary series with the original vaccine in seronegative PLWH resulted in a response that was only comparable to (and not greater than) seronegative PLWH who received later stage material for the first time as a primary series during the crossover, suggesting that while suboptimal priming by the original vaccine in seronegative PLWH could be boosted, it could not achieve levels exceeding those in seronegative PLWH primed with more optimal later stage vaccine (in spite of the fewer total doses in the latter). This pattern was not seen in HIV-negative participants, with boosted Day 201–seronegative HIV-negative participants achieving levels, as expected, nearly double those observed in newly primed Day 201–seronegative HIV-negative participants, suggesting a potential interaction of HIV status (even in those with well-controlled HIV) with the potency of an initial vaccine prime.

Due to high levels of SARS-CoV-2 infection in South Africa throughout multiple waves of the COVID-19 pandemic and during the follow-up period of this study, we observed a large proportion of participants who achieved hybrid immunity during the pre- and post-crossover/booster phases, with similarly high levels of NAb responses induced following either a primary series or booster dose of vaccine in previously infected participants.[18,23] Hybrid immunity is increasingly the most prevalent status of COVID-19–vaccinated populations worldwide with the convergence of vaccination and boosters, waning of vaccine-induced immunity, and ongoing emergence of highly transmissible immune-escaped variants such as Omicron and its sublineages. The benefits of hybrid immunity relative to either vaccine-induced or natural immunity alone, in both the pre-Omicron and Omicron periods has been demonstrated across multiple studies, countries, and vaccine platforms both in terms of the increase of protection against reinfection, and notably, in the extension of the durability and breadth of protection against emerging variants, including Omicron.[24–28] Although Omicron cross-neutralization studies of seropositive primary series and booster recipients in this study are underway, the pattern of homologous virus neutralizing antibody responses in seropositive participants, and the Omicron cross-neutralization data in boosted seronegative participants from this study reported in Bhiman et al.,[20] suggest that there is likely to be strong restoration of cross-neutralizing antibody responses against Omicron sublineages in primary series and booster vaccinated seropositive participants.

The booster dose had a similar safety profile to the primary series across serostatus and HIV status. Analysis of MAAEs, PIMMCs, AESIs, SAEs, and AEs leading to discontinuation found no consistent association with the booster.

Our study was subject to certain limitations. As these are results from a phase 2a/b study, clinical efficacy of the booster dose was not available for this report but will be reported on separately (as will data related to cell-mediated immunity). Additionally, most participants were aged 18–64 years and there was a relatively small proportion of participants who were >65 years of age. While we made every effort within the limits of available and practical methods, to identify persons who had SARS-CoV-2 infection by the time of the crossover period, it is impossible to completely exclude all exposed participants in the crossover seronegative population. Therefore, it is possible that unidentified infections might have contributed to some of the results. Cross-reactivity to VOC circulating at the time of the study have been previously reported for a subset of the total population;[20] however, were not investigated in the individual PLWH and HIV-negative cohorts at this time, but may be included in a future report. Also, we enrolled PLWH who we expected to be relatively immunocompetent, limiting the general applicability of the results to PLWH who might not be adequately managed on anti-retroviral therapy (ART). A future report of a separate study will include outcomes in PLWH with less well-controlled disease.

Overall, a single booster dose of NVX-CoV2373 administered approximately 6 months after the primary series induced a substantial increase in binding and neutralizing antibodies higher than those seen after the 2-dose primary series at Day 35, while also displaying an acceptable safety profile. These findings support the use of the vaccine in booster programs in all adult populations, including PLWH.

Acknowledgments

We thank all of the study participants who volunteered for this study. This study was funded by Novavax, Inc. and the Bill & Melinda Gates Foundation. Investigational vaccine manufacturing support was provided by the Coalition for Epidemic Preparedness Innovations. Medical writing, editing, and formatting support was provided by Kelly Cameron, PhD, CMPP, of Ashfield MedComms, and Anthony M. Marchese, PhD, of Novavax, Inc. We thank Andreana Robertson, MS, formerly of Novavax, Inc., for the biostatistical support of the study. Additionally, the authors thank Gertruida Kruger, MBChB, of MERC Research, Nazira Carrim-Ganey, MBBCh, of Newtown Clinical Research, and Sutika Bhika, MBBS, currently at Novartis, for their contributions to the study as Site Investigators.

Disclosure statement

SAM reports receiving grant support, paid to his institution, from BMGF, Novavax, Pfizer, GlaxoSmithKline, Minervax, MERK, providence, Gritstone, and ImmunityBio. QB reports receiving grant support, paid to his institution, from Wits Health Consortium, Bill & Melinda Gates Foundation, South African Medical Research Council, AstraZeneca Pharmaceuticals, Sinovac, Johnson & Johnson, and Pfizer. LFF reports receiving financial support from Novavax for trial procedures. LF reports receiving fees as a contractor and being a paid employee and stock shareholder of Novavax, Inc. GMG reports receiving fees as a consultant and being a paid employee and stock shareholder of Novavax, Inc. All authors who are or used to be employees of Novavax, Inc. may hold stock of Novavax, Inc. All other authors declare no competing interests.

Funding

The work was supported by Novavax, Inc., the Bill & Melinda Gates Foundation, and the Coalition for Epidemic Preparedness Innovations.

Notes on contributor

Dr. Vivek Shinde is Vice President, Clinical Development with responsibility of leading the clinical development programs for COVID-influenza combination and influenza vaccines. He is a research physician and biotech executive with specialty training in internal medicine, preventive medicine, global health, clinical research, and epidemiology from UCSF, Johns Hopkins, NYU, and the U.S. Centers for Disease Control. He has over a decade and a half of combined research and global health experience in influenza, RSV, and viral respiratory disease research, including vaccine clinical development (leading mid- and late-stage vaccine development programs), vaccine pharmacoepidemiology (leading large post-marketing safety and effectiveness trials), real world evidence research, and infectious disease epidemiology. Prior to joining Novavax in August 2015, he held various scientific and strategic leadership positions through key roles in public and private sector organizations at the local, national, and international levels, including the U.S.-CDC, the NYC DoH, WHO-HQ Geneva and GlaxoSmithKline Vaccines.

Declaration of Interests

Contributors

Medical writing, editing, and formatting support was provided by Kelly Cameron, PhD, CMPP, of Ashfield MedComms, an Inizio company, supported by Novavax, Inc. Additionally, medical writing and editing was provided by Anthony M. Marchese, PhD, of Novavax, Inc.

VS, IC, LF, CB, GMG, SN, and SAM were involved in the study design.

ALK, ZH, MA, QB, LF, UL, MSLM, DM, SH, LFF, CL, MT, NS, AG, KD, CG, NJ, JJL, RM, AEB, GB, FGP, NL, AP, PLV, AL, AE, FGP, AOJ, SF, KA, AT, DK, and SAM were involved in data collection.

GC and IC did the statistical analyses. SCC provided project management. MZ and JSP conducted data analysis and interpretation. VS and AM wrote the first draft of the manuscript. GA provided writing support and guidance.

VS, AM, GC, and IC have directly accessed and verified the data in this manuscript.

All authors were involved in data interpretation and reviewed, commented on, and approved this manuscript prior to submission for publication. The authors accept accountabilities for all aspects of the work, ensuring questions related to accuracy or integrity are investigated and resolved. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Anonymized participant data will be made available when the trial is complete, upon request directed to the sponsor. Proposals will be reviewed and approved by the sponsor on the basis of scientific merit. Upon approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. Full details of the approved trial protocol (version 6.0) are available online at https://www.novavax.com/resources.

References

1. Barouch DH. Covid-19 vaccines — immunity, variants, boosters. N Engl J Med. 2022;387(11):1011–1020. doi:10.1056/NEJMra2206573.
2. Young M, Crook H, Scott J, Edison P. Covid-19: virology, variants, and vaccines. BMJ Med. 2022;1(1):e000040. doi:10.1136/bmjmed-2021-000040.
3. Centers for Disease Control and Prevention. COVID data tracker. 2022 [accessed 2022 Nov 10]. https://covid.cdc.gov/covid-data-tracker/#variant-proportions.
4. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, Anyaneji UJ, Bester PA, Boni MF, Chand M, et al. Rapid epidemic expansion of the SARS-CoV-2 omicron variant in southern Africa. Nature. 2022;603(7902):679–686. doi:10.1038/s41586-022-04411-y.
5. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, Gower C, Kall M, Groves N, O'Connell A-M, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med. 2022;386(16):1532–1546. doi:10.1056/NEJMoa2119451.
6. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, Gallagher E, Thelwall S, Groves N, Dabrera G, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. N Engl J Med. 2022;386(4):340–350. doi:10.1056/NEJMoa2115481.
7. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, Ledgerwood JE, Mascola JR, Graham BS, Lin BC, et al. Antibody persistence through 6 Months after the Second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med. 2021;384(23):2259–2261. doi:10.1056/NEJMc2103916.
8. Pegu A, O'Connell SE, Schmidt SD, O'Dell S, Talana CA, Lai L, Albert J, Anderson E, Bennett H, Corbett KS, et al. Durability of mRNA-1273 vaccine–induced antibodies against SARS-CoV-2 variants. Science. 2021;373(6561):1372–1377. doi:10.1126/science.abj4176.
9. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, Alroy-Preis S, Ash N, Huppert A, Milo R, et al. Protection by a fourth dose of BNT162b2 against omicron in Israel. N Engl J Med. 2022;386(18):1712–1720. doi:10.1056/NEJMoa2201570.
10. Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, McGhee N, Tomassini JE, Chen X, Chang Y, et al. A bivalent omicron-containing booster vaccine against covid-19. N Engl J Med. 2022;387(14):1279–1291. doi:10.1056/NEJMoa2208343.
11. Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, Lewis N, Natarajan K, Stenehjem E, Grannis SJ, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-Associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance - VISION network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):255–263. doi:10.15585/mmwr.mm7107e2.
12. Hachmann NP, Miller J, Collier A-R, Barouch DH. Neutralization escape by SARS-CoV-2 omicron subvariant BA.4.6. N Engl J Med. 2022;387(20):1904–1906. doi:10.1056/NEJMc2212117.
13. Mallory RM, Formica N, Pfeiffer S, Wilkinson B, Marcheschi A, Albert G, McFall H, Robinson M, Plested JS, Zhu M, et al. Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomised, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2022;22(11):1565–1576. doi:10.1016/S1473-3099(22)00420-0.
14. Menni C, May A, Polidori L, Louca P, Wolf J, Capdevila J, Hu C, Ourselin S, Steves CJ, Valdes AM, et al. COVID-19 vaccine waning and effectiveness and side-effects of boosters: a prospective community study from the ZOE COVID study. Lancet Infect Dis. 2022;22(7):1002–1010. doi:10.1016/S1473-3099(22)00146-3.
15. Nemet I, Kliker L, Lustig Y, Zuckerman N, Erster O, Cohen C, Kreiss Y, Alroy-Preis S, Regev-Yochay G, Mendelson E, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. N Engl J Med. 2021;386(5):492–494. doi:10.1056/NEJMc2119358.
16. Dunkle LM, Kotloff KL, Gay CL, Áñez G, Adelglass JM, Barrat Hernández AQ, Harper WL, Duncanson DM, McArthur MA, Florescu DF, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. N Engl J Med. 2022;386(6):531–543. doi:10.1056/NEJMoa2116185.

17. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, Chadwick DR, Clark R, Cosgrove C, Galloway J, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med. 2021;385(13):1172–1183. doi:10.1056/NEJMoa2107659.
18. Madhi SA, Moodley D, Hanley S, Archary M, Hoosain Z, Lalloo U, Louw C, Fairlie L, Fouche LF, Masilela MSL, et al. Immunogenicity and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine in people living with and without HIV-1 infection: a randomised, controlled, phase 2A/2B trial. Lancet HIV. 2022;9(5):e309–e322. doi:10.1016/S2352-3018(22)00041-8.
19. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, Lalloo U, Masilela MSL, Moodley D, Hanley S, et al. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021;384(20):1899–1909. doi:10.1056/NEJMoa2103055.
20. Bhiman JN, Richardson SI, Lambson BE, Kgagudi P, Mzindle N, Kaldine H, Crowther C, Gray G, Bekker L-G, Koen A, et al. Novavax NVX-COV2373 triggers neutralization of omicron sub-lineages. Sci Rep. 2023;13(1):1222. doi:10.1038/s41598-023-27698-x.
21. Gray G, Collie S, Goga A, Garrett N, Champion J, Seocharan I, Bamford L, Moultrie H, Bekker L-G. Effectiveness of Ad26.COV2.S and BNT162b2 vaccines against omicron variant in South Africa. N Engl J Med. 2022;386(23):2243–2245. doi:10.1056/NEJMc2202061.
22. Fong Y, Huang Y, Benkeser D, Carpp LN, Áñez G, Woo W, McGarry A, Dunkle LM, Cho I, Houchens CR, Martins K. Immune correlates analysis of the PREVENT-19 COVID-19 vaccine efficacy clinical trial. medRxiv. 2022. 2022.06.22.22276362.
23. Madhi SA, Kwatra G, Myers JE, Jassat W, Dhar N, Mukendi CK, Nana AJ, Blumberg L, Welch R, Ngorima-Mabhena N, et al. Population immunity and covid-19 severity with omicron variant in South Africa. N Engl J Med. 2022;386(14):1314–1326. doi:10.1056/NEJMoa2119658.
24. Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, Al-Khatib HA, Smatti MK, Coyle P, Al-Kanaani Z, et al. Effects of previous infection and vaccination on symptomatic omicron infections. N Engl J Med. 2022;387(1):21–34. doi:10.1056/NEJMoa2203965.
25. Cerqueira-Silva T, de Araujo Oliveira V, Paixão ES, Florentino PTV, Penna GO, Pearce N, Werneck GL, Barreto ML, Boaventura VS, Barral-Netto M, et al. Vaccination plus previous infection: protection during the omicron wave in Brazil. Lancet Infect Dis. 2022;22(7):945–946. doi:10.1016/S1473-3099(22)00288-2.
26. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman LS, Ash N, Alroy-Preis S, Huppert A, Milo R. Protection and waning of natural and hybrid immunity to SARS-CoV-2. N Engl J Med. 2022;386(23):2201–2212. doi:10.1056/NEJMoa2118946.
27. Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A, Wellington E, Khawam J, Munro K, Cole M, et al. Protection against SARS-CoV-2 after covid-19 vaccination and previous infection. N Engl J Med. 2022;386(13):1207–1220. doi:10.1056/NEJMoa2118691.
28. Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. Lancet Infect Dis. 2022;22(6):781–790. doi:10.1016/S1473-3099(22)00143-8.