ORIGINAL ARTICLE

# Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant

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## ABSTRACT

### BACKGROUND

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants threatens progress toward control of the coronavirus disease 2019 (Covid-19) pandemic. In a phase 1–2 trial involving healthy adults, the NVX-CoV2373 nanoparticle vaccine had an acceptable safety profile and was associated with strong neutralizing-antibody and antigen-specific polyfunctional CD4+ T-cell responses. Evaluation of vaccine efficacy was needed in a setting of ongoing SARS-CoV-2 transmission.

### METHODS

In this phase 2a–b trial in South Africa, we randomly assigned human immunodeficiency virus (HIV)–negative adults between the ages of 18 and 84 years or medically stable HIV-positive participants between the ages of 18 and 64 years in a 1:1 ratio to receive two doses of either the NVX-CoV2373 vaccine (5 μg of recombinant spike protein with 50 μg of Matrix-M1 adjuvant) or placebo. The primary end points were safety and vaccine efficacy against laboratory-confirmed symptomatic Covid-19 at 7 days or more after the second dose among participants without previous SARS-CoV-2 infection.

### RESULTS

Of 6324 participants who underwent screening, 4387 received at least one injection of vaccine or placebo. Approximately 30% of the participants were seropositive for SARS-CoV-2 at baseline. Among 2684 baseline seronegative participants (94% HIV-negative and 6% HIV-positive), predominantly mild-to-moderate Covid-19 developed in 15 participants in the vaccine group and in 29 in the placebo group (vaccine efficacy, 49.4%; 95% confidence interval [CI], 6.1 to 72.8). Vaccine efficacy among HIV-negative participants was 60.1% (95% CI, 19.9 to 80.1). Of 41 sequenced isolates, 38 (92.7%) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0% (95% CI, −0.6 to 76.2) among the HIV-negative participants. Preliminary local and systemic reactogenicity events were more common in the vaccine group; serious adverse events were rare in both groups.

### CONCLUSIONS

The NVX-CoV2373 vaccine was efficacious in preventing Covid-19, with higher vaccine efficacy observed among HIV-negative participants. Most infections were caused by the B.1.351 variant. (Funded by Novavax and the Bill and Melinda Gates Foundation; ClinicalTrials.gov number, NCT04533399.)

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THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic, caused by the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had resulted in more than 144 million documented cases and 3 million deaths worldwide as of April 23, 2021.[1,2] Vaccination remains a cornerstone of control strategies. Current vaccines primarily target the SARS-CoV-2 spike protein on the basis of the prototype Wuhan strain.[3] The messenger RNA (mRNA) vaccines (BNT162b2 and mRNA-1273) have shown vaccine efficacy of 94 to 95%[4,5] against Covid-19 of any severity, and corresponding vaccine efficacy for vector-based vaccines has been reported to be 70% for ChAdOx1 nCoV-19, 92% for Gam-COVID-Vac, and 67% for Ad26.COV2.S, with the Ad26.COV2.S vaccine measured against moderate-to-severe Covid-19.[6-8]

Among the Covid-19 vaccines under development is a recombinant SARS-CoV-2 nanoparticle vaccine (NVX-CoV2373, Novavax). The vaccine is produced by engineering a baculovirus that contains a gene encoding full-length SARS-CoV-2 spike glycoprotein (prototype Wuhan-Hu-1 sequence) stabilized in the prefusion conformation. Cultures of cells obtained from the *Spodoptera frugiperda* moth are infected with recombinant baculovirus to express SARS-CoV-2 spike protein trimers, which are then extracted and chromatographically purified. When formulated with polysorbate 80 (PS 80), the purified trimers assemble into protein nanoparticles consisting of rosettes of spike trimers held together by hydrophobic interactions with a PS 80 micellar core. The nanoparticles are then further coformulated with the saponin-based adjuvant Matrix-M1.[9,10] In an ongoing randomized, placebo-controlled, phase 1–2 trial involving healthy adults, the NVX-CoV2373 vaccine, administered in a two-dose regimen 21 days apart, had an acceptable safety profile and was associated with a strong antigen-specific polyfunctional CD4+ T-cell response and induced a neutralizing-antibody level that was four times the level in convalescent serum obtained from patients with predominantly moderate-to-severe Covid-19.[11]

Recent reports from the United Kingdom, Brazil, and South Africa on the emergence of the B.1.1.7, P1, and B.1.351 (N501Y.V2) variants, respectively, confirm the acquisition of mutations in key antigenic sites in the receptor-binding domain and N-terminal domain of the spike protein.[12-17] These antigenic changes may render naturally acquired or vaccine-derived immunity to prototype-like virus less effective against subsequent infection with variant viruses.[13,17-19] Here, we describe early findings on the primary efficacy end point and preliminary safety of a randomized, observer-blinded, placebo-controlled, phase 2a–b trial of NVX-CoV2373 in South Africa during a period of predominant circulation of the B.1.351 variant virus.

## METHODS

### TRIAL DESIGN AND PARTICIPANTS

From August 17, 2020, through November 25, 2020, we enrolled participants at 16 sites in South Africa. The trial was designed to provide a preliminary evaluation of vaccine safety and efficacy during ongoing pandemic transmission of SARS-CoV-2. Participants were healthy adults between the ages of 18 and 84 years without human immunodeficiency virus (HIV) infection or a subgroup of adults between the ages of 18 and 64 years with HIV infection whose condition was medically stable. Baseline IgG antibodies against the spike protein (anti-spike IgG antibodies) were measured at study entry to help determine baseline SARS-CoV-2 serostatus for the analysis of vaccine efficacy. As a safety measure, enrollment was staggered into stage 1 (defined by the first third of targeted enrollment) and stage 2 (the remainder of enrollment) for both HIV-negative and HIV-positive participants. Progression from stage 1 to stage 2 in each group required a favorable review of safety data through day 7 from the previous stage against prespecified rules that would trigger a pause in vaccine administration. (Details regarding the participants in each stage are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Key exclusion criteria were pregnancy, long-term receipt of immunosuppressive therapy, autoimmune or immunodeficiency disease except for medically stable HIV infection, a history of confirmed or suspected Covid-19, and SARS-CoV-2 infection as confirmed on a nucleic acid amplification test (NAAT) performed as part of screening within 5 days before anticipated initial administration of the vaccine or placebo. All the participants provided written informed consent before enrollment. Additional details regarding

the trial design, conduct, oversight, and analyses are provided in the Supplementary Appendix and the protocol (which includes the statistical analysis plan), available at NEJM.org.

### OVERSIGHT

The NVX-CoV2373 vaccine was developed by Novavax, which sponsored the trial and was responsible for the overall design (with input from the lead investigator), site selection, monitoring, and analysis. Trial investigators were responsible for data collection. The protocol was approved by the South African Health Products Regulatory Authority and by the institutional review board at each trial center. Oversight of safety, which included monitoring for specific vaccination-pause rules, was performed by an independent safety monitoring committee.

The first author wrote the first draft of the manuscript with assistance from a medical writer who is an author and an employee of Novavax. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to receive two intramuscular injections, 21 days apart, of either NVX-CoV2373 (5 μg of recombinant spike protein with 50 μg of Matrix-M1 adjuvant) or saline placebo (injection volume, 0.5 ml), administered by staff members who were aware of trial-group assignments but were not otherwise involved with other trial procedures or data collection. All other staff members and trial participants remained unaware of trial-group assignments. Participants were scheduled for in-person follow-up visits on days 7, 21, and 35 and at 3 months and 6 months to collect vital signs, review any adverse events, discuss changes in concomitant medications, and obtain blood samples for immunogenicity analyses. A follow-up telephone visit was scheduled for 12 months after vaccination.

### SAFETY ASSESSMENTS

The primary safety end points were the occurrence of all unsolicited adverse events, including those that were medically attended, serious, or of special interest, through day 35 (Tables S2 and S3) and solicited local and systemic adverse events that were evaluated by means of a reactogenicity diary for 7 days after each vaccination (Tables S4 and S5). Safety follow-up was ongoing through month 12.

### EFFICACY ASSESSMENTS

The primary efficacy end point was confirmed symptomatic Covid-19 that was categorized as mild, moderate, or severe (hereafter called symptomatic Covid-19) and that occurred within 7 days after receipt of the second injection (i.e., after day 28) (Table S6). Starting on day 8 and continuing through 12 months, we performed active surveillance (telephone calls every 2 weeks from trial sites to participants) and passive surveillance (telephone contact at any time from participants to trial sites) for symptoms of suspected Covid-19 (Table S7 and Fig. S1). A new onset of suspected symptoms of Covid-19 triggered initial in-person and follow-up surveillance visits to perform clinical assessments (vital signs, including pulse oximetry, and a lung examination) and for collection of nasal swabs (Fig. S2). In addition, suspected Covid-19 symptoms were also assessed and nasal swabs collected at all scheduled trial visits. Nasal-swab samples were tested for the presence of SARS-CoV-2 by NAAT with the use of the BD MAX system (Becton Dickinson). We used the InFLUenza Patient-Reported Outcome (FLU-PRO) questionnaire to comprehensively assess symptoms for the first 10 days of a suspected episode of Covid-19.

### WHOLE-GENOME SEQUENCING

In a blinded fashion, we performed post hoc whole-genome sequencing of nasal samples obtained from all the participants who had symptomatic Covid-19. Details regarding the whole-genome sequencing methods and phylogenetic analysis are provided in Fig. S3.

### STATISTICAL ANALYSIS

The safety analysis population included all the participants who had received at least one injection of NVX-CoV2373 or placebo; regardless of group assignment, participants were evaluated according to the intervention they had actually received. Safety analyses were presented as numbers and percentages of participants who had solicited local and systemic adverse events through day 7 after each vaccination and who had unsolicited adverse events through day 35.

We performed a per-protocol efficacy analysis in the population of participants who had been seronegative for SARS-CoV-2 at baseline and who had received both injections of NVX-CoV2373 or placebo as assigned, had no evidence of SARS-CoV-2 infection (by NAAT or anti-spike IgG analysis) within 7 days after the second injection (i.e., before day 28), and had no major protocol deviations affecting the primary efficacy outcome. A second per-protocol efficacy analysis population was defined in a similar fashion except that participants who were seropositive for SARS-CoV-2 at baseline could be included.

Vaccine efficacy (calculated as a percentage) was defined as $(1-RR)\times100$, where RR is the relative risk of Covid-19 illness in the vaccine group as compared with the placebo group. The official, event-driven efficacy analysis targeted a minimum number of 23 end points (range, 23 to 50) to provide approximately 90% power to detect vaccine efficacy of 80% on the basis of an incidence of symptomatic Covid-19 of 2 to 6% in the placebo group. This analysis was performed at an overall one-sided type I error rate of 0.025 for the single primary efficacy end point. The relative risk and its confidence interval were estimated with the use of Poisson regression with robust error variance. Hypothesis testing of the primary efficacy end point was performed against the null hypothesis of vaccine efficacy of 0%. The success criterion required rejection of the null hypothesis to show a statistically significant vaccine efficacy.

## RESULTS

### PARTICIPANTS

Of the 6324 participants who underwent screening, 4387 received at least one injection of NVX-CoV2373 or placebo (2199 in the vaccine group and 2188 in the placebo group); 4332 participants received both injections (Fig. 1).

Demographic and baseline characteristics were well balanced in the two groups (Table 1). The mean age of all participants was 32.0 years, and 4.2% of the participants in each group were between the ages of 65 and 84 years. Approximately 57% of the participants were men, and most were Black African (95.3%). Twenty percent of the participants were obese, 5.6% had hypertension, and 1.6% had type 2 diabetes. Approximately 30% of the participants were seropositive
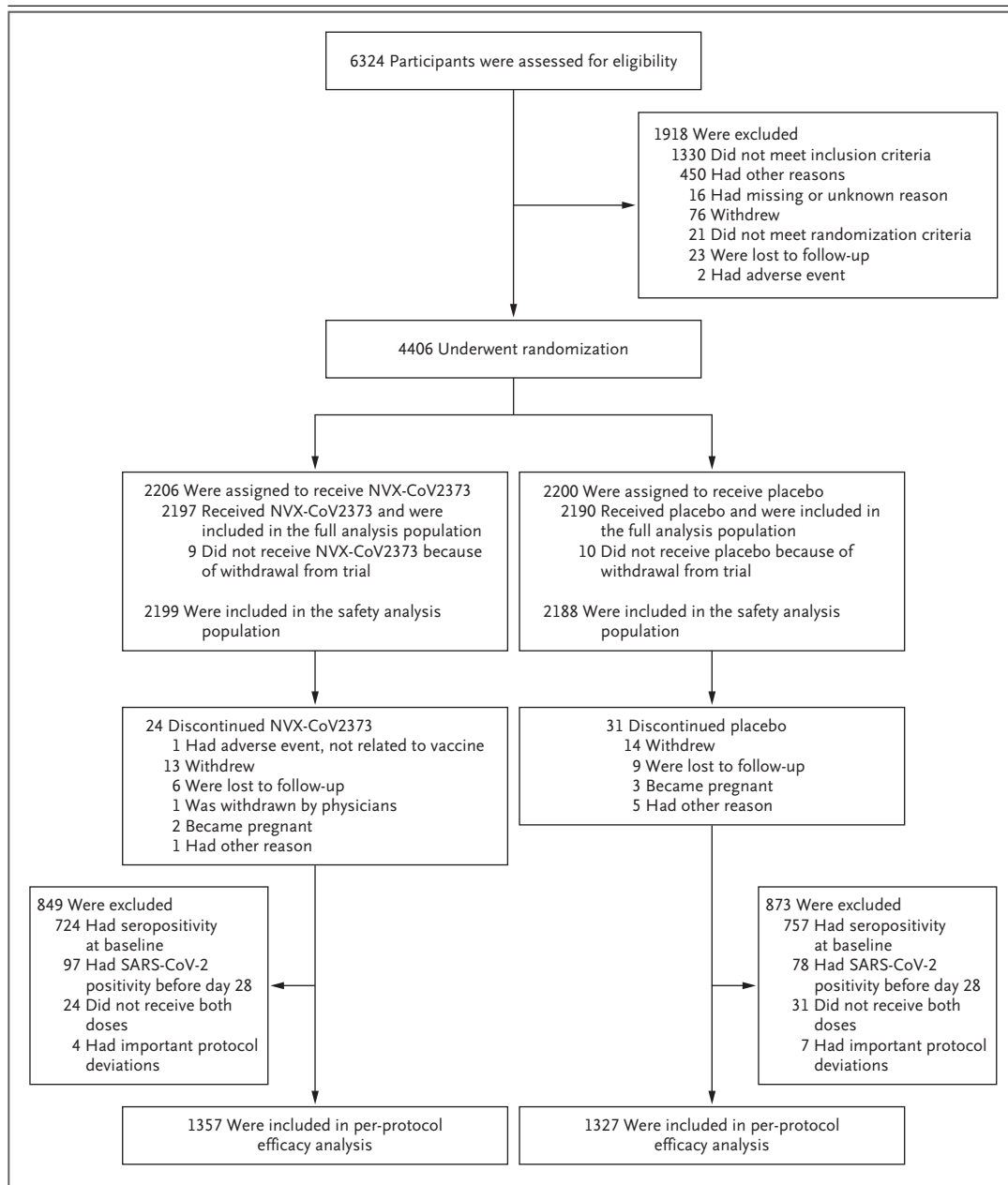
**Figure 1 (facing page). Enrollment and Outcomes.**

The full analysis set included all the participants who had undergone randomization and who had received at least one dose of the NVX-CoV2373 vaccine or placebo, regardless of protocol violations or missing data; data were analyzed according to the assigned trial group. The safety analysis set included all the participants who had received at least one dose of NVX-CoV2373 or placebo, with participants assessed according to the trial injection they actually received. Among the participants who were excluded from participating in the trial, approximately 32% had positive results on testing for human immunodeficiency virus (HIV) at screening, 18% had a history of suspected or diagnosed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, 11% had an exclusionary chronic medical condition, 9% had an exclusionary high or low body-mass index, 7% could not provide informed consent, and 5% had acute or ongoing illness. Among the participants who were excluded for other reasons, approximately 69% were otherwise eligible but had missed the time window for enrollment in a particular stage or cohort; in 23% of the participants, the reason for exclusion was not specified. The data-cutoff date for the primary efficacy analysis was January 8, 2021, which represented a median follow-up of 66 days after the first dose and 45 days after the second dose. The data-cutoff date for the primary safety analysis was January 25, 2021, which included safety data through 35 days after the first dose in all 968 stage 1 participants (889 who were HIV-negative and 79 who were HIV-positive).

at baseline according to an evaluation of anti-spike IgG antibodies (with a sensitivity of 94.7% and a specificity of 96.4% at a predefined anti-spike IgG threshold). (Details regarding the anti-spike IgG threshold determination are provided in the Supplementary Appendix.)

### SAFETY

Preliminary safety data were available on all stage 1 participants, which included the first 889 HIV-negative participants and the first 80 HIV-positive participants who had completed safety follow-up through at least day 35 at the time of the cutoff date for the primary efficacy analysis (Table S8). Briefly, solicited local and systemic adverse events, which were predominantly mild to moderate and transient, were more common in the vaccine group than in the placebo group. After the first dose, the most frequently reported solicited local adverse event was injection-site pain (in 37% of the participants who were seronegative at baseline and 39% of those who were seropositive in the vaccine group, and in 15% and 16% of the partici-

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│  6324 Participants were assessed for     │
│  eligibility                             │
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                    │
                    │        ┌──────────────────────────────────────────┐
                    │        │ 1918 Were excluded                       │
                    ├───────▶│   1330 Did not meet inclusion criteria   │
                    │        │    450 Had other reasons                 │
                    │        │     16 Had missing or unknown reason      │
                    │        │     76 Withdrew                          │
                    │        │     21 Did not meet randomization criteria│
                    │        │     23 Were lost to follow-up            │
                    │        │      2 Had adverse event                 │
                    │        └──────────────────────────────────────────┘
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│  4406 Underwent randomization            │
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| 2206 Were assigned to receive NVX-CoV2373<br>2197 Received NVX-CoV2373 and were included in the full analysis population<br>9 Did not receive NVX-CoV2373 because of withdrawal from trial<br><br>2199 Were included in the safety analysis population | 2200 Were assigned to receive placebo<br>2190 Received placebo and were included in the full analysis population<br>10 Did not receive placebo because of withdrawal from trial<br><br>2188 Were included in the safety analysis population |
|---|---|
| 24 Discontinued NVX-CoV2373<br>1 Had adverse event, not related to vaccine<br>13 Withdrew<br>6 Were lost to follow-up<br>1 Was withdrawn by physicians<br>2 Became pregnant<br>1 Had other reason | 31 Discontinued placebo<br>14 Withdrew<br>9 Were lost to follow-up<br>3 Became pregnant<br>5 Had other reason |

| 849 Were excluded<br>724 Had seropositivity at baseline<br>97 Had SARS-CoV-2 positivity before day 28<br>24 Did not receive both doses<br>4 Had important protocol deviations | 873 Were excluded<br>757 Had seropositivity at baseline<br>78 Had SARS-CoV-2 positivity before day 28<br>31 Did not receive both doses<br>7 Had important protocol deviations |
|---|---|
| 1357 Were included in per-protocol efficacy analysis | 1327 Were included in per-protocol efficacy analysis |

pants, respectively, in the placebo group) (Table S9). The incidence of solicited local adverse events after the second dose was similar to that after the first dose, with a mean duration (generally <3 days) that was slightly longer after the second dose. Severe local adverse events were infrequent but occurred more often after the second dose among the seronegative participants in the vaccine group than in the placebo group (4% vs. 1%).

Among the vaccine recipients, the most com-mon solicited systemic adverse events after the first dose and second dose were headache (20 to 25%), muscle pain (17 to 20%), and fatigue (12 to 16%). The mean duration of such events was slightly longer after the second dose but gener-ally less than 3 days. Among the participants who were seronegative at baseline, grade 3 sys-temic adverse events were infrequent but were more common in the vaccine group after the second dose (4%) than after the first dose (2%), although the incidence was similar to that in the

**Table 1. Characteristics of the Participants at Baseline (Safety Population).***

| Characteristic | Vaccine Group (N=2199) | Placebo Group (N=2188) | All Participants (N=4387) |
|---|---|---|---|
| Age | | | |
| Mean — yr | 31.9±12.9 | 32.2±13.0 | 32.0±13.0 |
| Median — yr | 28.0 | 28.0 | 28.0 |
| Distribution — no. (%) | | | |
| 18–64 yr | 2104 (95.7) | 2094 (95.7) | 4198 (95.7) |
| 65–84 yr | 92 (4.2) | 92 (4.2) | 184 (4.2) |
| Missing data | 3 (0.1) | 2 (0.1) | 5 (0.1) |
| Sex — no. (%) | | | |
| Male | 1252 (56.9) | 1266 (57.9) | 2518 (57.4) |
| Female | 947 (43.1) | 922 (42.1) | 1869 (42.6) |
| Race — no. (%)† | | | |
| Black | 2098 (95.4) | 2082 (95.2) | 4180 (95.3) |
| White | 86 (3.9) | 66 (3.0) | 152 (3.5) |
| Other | 40 (1.8) | 49 (2.2) | 89 (2.0) |
| Body-mass index‡ | | | |
| Mean | 25.1±6.0 | 25.0±5.9 | 25.0±6.0 |
| 30 to 40 — no. (%) | 451 (20.5) | 440 (20.1) | 891 (20.3) |
| Coexisting condition — no. (%) | | | |
| Hypertension | 125 (5.7) | 119 (5.4) | 244 (5.6) |
| Type 2 diabetes | 31 (1.4) | 39 (1.8) | 70 (1.6) |
| Seropositivity for SARS-CoV-2 — no. (%) | | | |
| Nucleic acid amplification test | 63 (2.9) | 63 (2.9) | 126 (2.9) |
| Anti-spike immunoglobulin G assay | 651 (29.6) | 673 (30.8) | 1324 (30.2) |

\* Plus–minus values are means ±SD. The NVX-CoV2373 vaccine consists of 5 $\mu$g of recombinant spike protein with 50 $\mu$g of Matrix-M1 adjuvant.
† Race was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

placebo group (4%), particularly with respect to fatigue and headache (Tables S8 and S9). Reactogenicity was generally similar among seronegative and seropositive vaccine recipients.

Medically attended adverse events (Table S10) and serious adverse events (Table S11) were infrequent but occurred more often in the vaccine group than in the placebo group (13 vs. 6 medically attended adverse events and 2 vs. 1 serious adverse events). There was no apparent clustering of specific adverse events according to intervention group, preferred term, or system organ class. To date, no serious adverse events have been assessed by trial investigators as being related to the vaccine (Table S8). No prespecified vaccination-pause rules were triggered.

## EFFICACY

Among the 2684 participants who were seronegative at baseline (94% who were HIV-negative and 6% who were HIV-positive) and who could be evaluated in the analysis of the primary efficacy end point after day 28, symptomatic Covid-19 was observed in 15 participants in the vaccine group and in 29 participants in the placebo group. These findings corresponded to a vaccine efficacy of 49.4% (95% confidence interval [CI], 6.1 to 72.8), which met the criterion for efficacy in the primary phase 2b evaluation (Table 2 and Fig. 2A). All the cases of Covid-19 in the per-protocol analysis were mild to moderate, except for one severe case in the placebo group.

Among the participants who were HIV-nega-

**Table 2. Vaccine Efficacy against Symptomatic Covid-19 at Least 7 Days after the Second Dose (Day 28).***

| Population and Baseline Anti-Spike IgG Serostatus | No. of Cases | Vaccine Group | | Placebo Group | | Vaccine Efficacy (95% CI)† |
|---|---|---|---|---|---|---|
| | | no./total no. | % (95% CI) | no./total no. | % (95% CI) | % |
| **All participants** | | | | | | |
| Seronegative at baseline: primary end point | 44 | 15/1357 | 1.1 (0.6 to 1.8) | 29/1327 | 2.2 (1.5 to 3.1) | 49.4 (6.1 to 72.8) |
| Seropositive at baseline | 19 | 6/500 | 1.2 (0.4 to 2.6) | 13/514 | 2.5 (1.4 to 4.3) | 52.6 (−23.8 to 81.8) |
| Any serostatus at baseline | 63 | 21/1857 | 1.1 (0.7 to 1.7) | 42/1841 | 2.3 (1.6 to 3.1) | 50.4 (16.6 to 70.5) |
| **HIV-negative participants** | | | | | | |
| Seronegative at baseline | 38 | 11/1281 | 0.9 (0.4 to 1.5) | 27/1255 | 2.2 (1.4 to 3.1) | 60.1 (19.9 to 80.1) |
| Seropositive at baseline | 19 | 6/467 | 1.3 (0.5 to 2.8) | 13/484 | 2.7 (1.4 to 4.5) | 52.2 (−24.8 to 81.7) |
| Any serostatus at baseline | 57 | 17/1748 | 1.0 (0.6 to 1.6) | 40/1739 | 2.3 (1.6 to 3.1) | 57.7 (25.7 to 75.9) |

* Symptomatic coronavirus disease 2019 (Covid-19) was confirmed by means of nucleic acid amplification testing. Data are listed for the primary per-protocol analysis population (which included participants who were seronegative for SARS-CoV-2 at baseline) and the secondary per-protocol analysis population (which included all the participants regardless of serostatus at baseline). HIV denotes human immunodeficiency virus.
† The 95% confidence interval for vaccine efficacy was calculated by means of the exact Clopper–Pearson method.

tive (a subgroup of the primary efficacy end point), symptomatic Covid-19 was observed in 11 participants in the vaccine group and in 27 participants in the placebo group among those who were seronegative at baseline, which corresponded to a vaccine efficacy of 60.1% (95% CI, 19.9 to 80.1) (Table 2 and Fig. 2B); the corresponding vaccine efficacy estimate was 52.2% (95% CI, −24.8 to 81.7) among those who were seropositive at baseline.

Among the participants who were HIV-positive and seronegative at baseline (another subgroup of the primary efficacy end point), symptomatic Covid-19 was observed in 4 of 76 participants in the vaccine group and in 2 of 72 participants in the placebo group. No cases were observed among the participants who were HIV-positive and seropositive at baseline in either group (33 in the vaccine group and 30 in the placebo group).

Among the participants who were seronegative at baseline, the 44 cases of symptomatic Covid-19 in the two groups occurred between November 23 and December 30, 2020. Of these participants, 41 (93%) had samples that were adequate for whole-genome sequencing; samples from 3 participants in the placebo group could not be sequenced. Of the 41 samples, the B.1.351 variant was identified in 38 (93%), which mirrored the national incidence during the same period (Fig. 2D and Fig. S1). In a post hoc analy-

sis, vaccine efficacy against the B.1.351 variant was 51.0% (95% CI, −0.6 to 76.2) among the HIV-negative participants (11 in the vaccine group and 22 in the placebo group) and 43.0% (95% CI, −9.8 to 70.4) in the combined HIV-negative and HIV-positive population (14 participants and 24 participants, respectively).

Notably, during the initial 60 days of follow-up in the placebo group, the preliminary incidence of Covid-19 that was observed among participants who were seronegative at baseline (5.3%; 95% CI, 4.3 to 6.6), which included 33 mild and 47 moderate cases among 1516 participants, was similar to the incidence among seropositive participants (5.2%; 95% CI, 3.6 to 7.2), which included 14 mild and 21 moderate cases among 674 participants (Fig. 2C).

## DISCUSSION

We describe preliminary evidence of the efficacy of a two-dose regimen of NVX-CoV2373 nanoparticle vaccine in preventing symptomatic Covid-19 during predominant transmission of the B.1.351 variant in South Africa.[12,15] The vaccine fulfilled the primary objective by showing significant vaccine efficacy of 49.4% among participants who were seronegative for SARS-CoV-2 at baseline regardless of HIV serostatus. Among the 94% of participants without HIV infection, the vaccine efficacy was 60.1%. The trial was not powered to
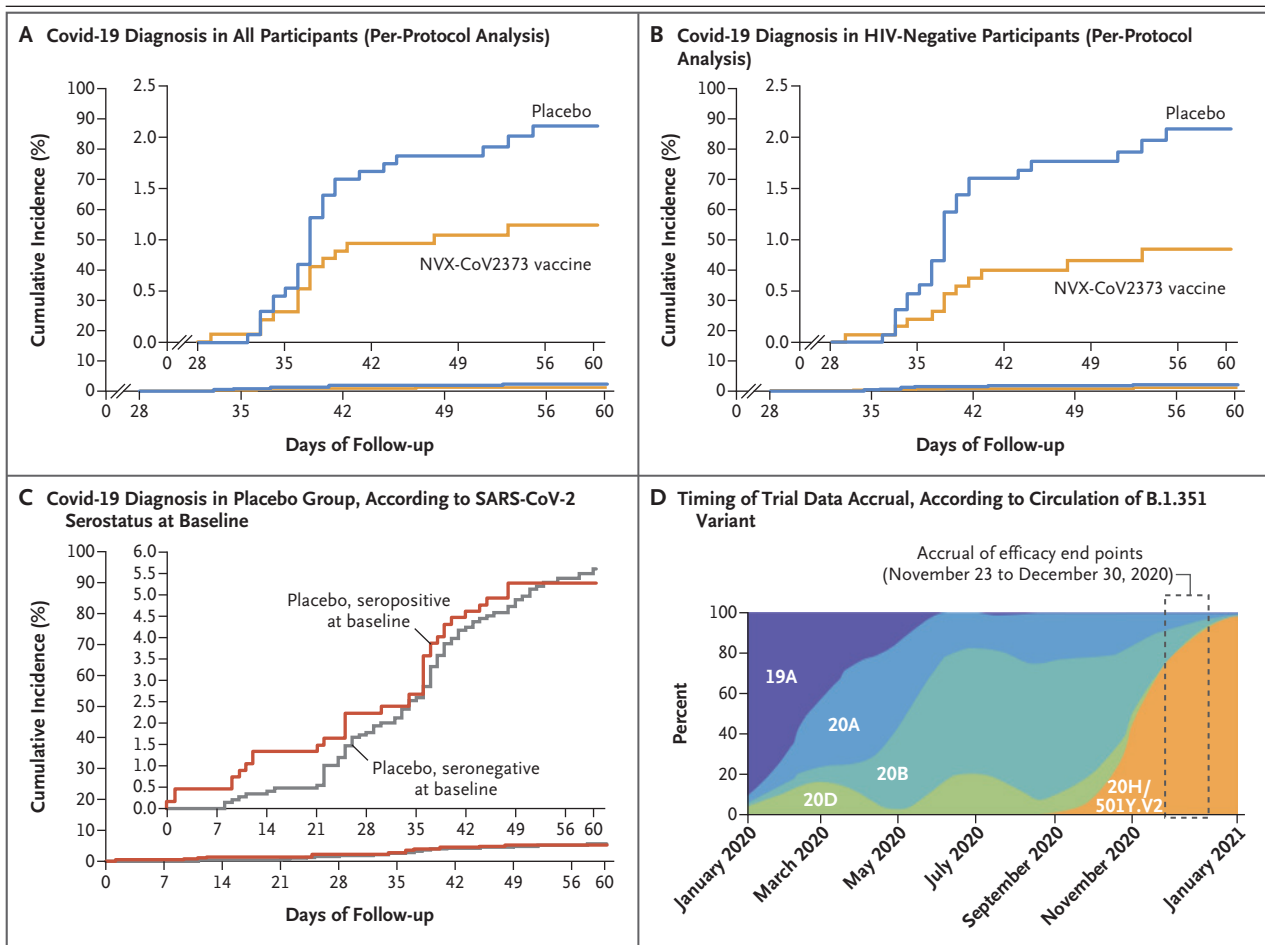
**Figure 2. Kaplan–Meier Analysis of NVX-CoV2373 Efficacy against Symptomatic Covid-19 and Timing of Trial Data Accrual.**

Shown is the cumulative incidence of symptomatic coronavirus disease 2019 (Covid-19) among the trial participants who were seronegative for SARS-CoV-2 at baseline 7 days after the administration of the second dose of NVX-CoV2373 vaccine or placebo (i.e., day 28) in the per-protocol analysis set, regardless of HIV serostatus (primary efficacy end point) (Panel A) and among the participants who were HIV-negative at baseline (a subgroup of the primary efficacy end point) (Panel B). Also shown is the incidence among participants in the placebo group who were seronegative for SARS-CoV-2 at baseline as compared with those who were seropositive at baseline in the full analysis set starting on day 0 (Panel C). The full analysis set included all the participants who had undergone randomization and who had received at least one dose of NVX-CoV2373 or placebo, regardless of protocol violations or missing data. In Panels A, B, and C, the insets show the data on an expanded y axis. The period of accrual of trial data for the per-protocol analysis of the efficacy end points is indicated by the dashed-line box, relative to the background circulation of the B.1.351 variant (noted here as clade 20H/501Y.V2) in South Africa (Panel D). Data regarding viral circulation are shown according to phylogenetic clade (19A, 20B, etc.) and percent circulation of each clade according to calendar time. Data have been adapted from Nextstrain.org and are freely available under the terms of the GNU Affero General Public License.

detect efficacy in the small population of participants with HIV infection. Preliminary safety data continued to indicate an acceptable safety and reactogenicity profile.[11]

In this placebo-controlled vaccine trial, we found that previous infection with first-wave prototype-like, pre-B.1.351 viruses did not appear to reduce the risk of Covid-19 due to subsequent infection with B.1.351 variants among placebo recipients during the initial 2 months of follow-up. This finding is preliminary and may have public health implications for pandemic modeling, control strategies, and vaccine development and deployment efforts. It is also consistent with the lack of incremental benefit conferred by preexisting immunity in vaccine recipients as evidenced in our trial by consistent levels of efficacy regardless of baseline serostatus for

SARS-CoV-2. Although these findings require further confirmation, our observations suggest that vaccination with prototype-sequenced NVX-CoV2373 conferred a degree of cross-protection against an immunologic escape variant.

Factors that may have created a milieu that was favorable to the emergence of the B.1.351 variant in South Africa include intense transmission during the first wave of infection, high levels of resulting immunity to prototype variants (as observed in our trial and corroborated in serosurveys[20]), and an ongoing high force of infection in advance of the second wave. The B.1.351 variant is reported to have emerged in the Eastern Cape Province of the country in October 2020 and rapidly spread to become the dominant circulating strain throughout the country during November and December 2020,[15] a period that coincided with the surge of second-wave transmission nationally. In our trial, which was conducted at sites that were dispersed across the country, we observed 44 cases of symptomatic Covid-19 between November 23 and December 30, 2020. Sequencing of nasal samples from participants with confirmed Covid-19 showed a pattern consistent with national molecular epidemiologic features.

The B.1.351 variant is characterized by three deleterious mutations at key antigenic sites in the receptor-binding domain, including N501Y, K417N, and E484K, with the latter two having particular functional effect.[13,15,17,18] The N501Y mutant is known to increase binding affinity of the spike protein to the human angiotensin-converting enzyme 2 receptor[21] and has been reported to increase transmissibility of the B.1.1.7 variant that was first identified in the United Kingdom.[16] The E484K mutant has been reported to abolish or substantially reduce neutralization by multiple potent monoclonal antibodies and polyclonal convalescent serum on both wild-type and pseudovirus neutralization assays.[12,13,17,18,22] In addition, postvaccination serum obtained from volunteers who had received either of the two mRNA vaccines that are currently being administered had reductions by a factor of 6.5 to 8.6 in neutralizing capacity to the B.1.351 variant relative to prototype virus on pseudovirus neutralization assays[17]; however, the effect of this finding on clinical efficacy has not been assessed. Wild-type and pseudovirus neutralization assays assessing the effect of the B.1.351 variant on the neutralizing capacity of NVX-CoV2373 vaccine-elicited antibodies are in progress. Nevertheless, our data provide clinical evidence of cross-protection against antigenically drifted viruses. In the interim analysis of our phase 3 trial being conducted in the United Kingdom, relatively high levels of efficacy were observed against both the matched prototype-like, prevariant strains (vaccine efficacy, 96%) and the B.1.1.7 variant (vaccine efficacy, 86%).[23] The high vaccine efficacy against the B.1.1.7 variant is consistent with the expected limited effect of the characteristic N501Y mutant (without a concomitant E484K mutant) on in vitro neutralization capacity of convalescent serum derived from prototype-like virus infections.[13,17]

Investigators have recently reported efficacy results of two other trials that have been partially or wholly conducted in South Africa and that are contemporaneous with circulation of the B.1.351 variant. In a large, multinational, phase 3 trial evaluating the efficacy of a single dose of the Ad26.COV2.S vaccine (Johnson & Johnson/Janssen), efficacy against moderate-to-severe Covid-19 among 6576 participants in South Africa was 52% at 14 days and 64% at 28 days after the first dose, with 95% of cases reportedly due to the B.1.351 variant. Vaccine efficacy against all-severity Covid-19 specific to the B.1.351 variant has not yet been reported, precluding a direct comparison with other vaccines.[8,24] In the second trial, the ChAdOx1 nCoV-19 vaccine (AstraZeneca) was evaluated in a phase 2 trial involving 2026 participants in South Africa in a population resembling that in our trial. Cases of Covid-19 among vaccine recipients were predominantly mild to moderate, with a reported overall vaccine efficacy of 22% (95% CI, −50 to 60) and an efficacy of 10% (95% CI, −77 to 55) against the B.1.351 variant, with the B.1.351 variant making up 95% of cases.[25]

Our trial has several limitations. The efficacy results are preliminary, with a median follow-up of 66 days after the first dose and 45 days after the second dose, and are limited in scope to the primary end point and subgroups of the primary end point, along with a post hoc analysis of B.1.351 variant sequencing data. Thus, caution is warranted in the interpretation of our results on the breadth of natural immunity and vaccine effects in the HIV-positive cohort, which represents a relatively small fraction of the trial popu-

lation. At the time of analysis, trial investigators had captured almost exclusively mild-to-moderate Covid-19 end points in a predominantly young, healthy population; consequently, we have not as yet been able to report on vaccine efficacy against severe Covid-19. Most large trials of vaccine efficacy against Covid-19 have reported notably higher vaccine efficacy against severe disease than against mild-to-moderate disease.[4-7] Additional follow-up may shed light on whether naturally acquired immunity to prototype-like virus alters the severity of infection caused by variant viruses.

We have found that a prototype-sequenced NVX-CoV2373 vaccine was efficacious and induced notable cross-protection during a pandemic with a dominant circulation of the B.1.351 variant.

## APPENDIX

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