ORIGINAL ARTICLE

Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Early clinical data from studies of the NVX-CoV2373 vaccine (Novavax), a recombinant nanoparticle vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that contains the full-length spike glycoprotein of the prototype strain plus Matrix-M adjuvant, showed that the vaccine was safe and associated with a robust immune response in healthy adult participants. Additional data were needed regarding the efficacy, immunogenicity, and safety of this vaccine in a larger population.

METHODS

In this phase 3, randomized, observer-blinded, placebo-controlled trial conducted at 33 sites in the United Kingdom, we assigned adults between the ages of 18 and 84 years in a 1:1 ratio to receive two intramuscular 5-μg doses of NVX-CoV2373 or placebo administered 21 days apart. The primary efficacy end point was virologically confirmed mild, moderate, or severe SARS-CoV-2 infection with an onset at least 7 days after the second injection in participants who were serologically negative at baseline.

RESULTS

A total of 15,187 participants underwent randomization, and 14,039 were included in the per-protocol efficacy population. Of the participants, 27.9% were 65 years of age or older, and 44.6% had coexisting illnesses. Infections were reported in 10 participants in the vaccine group and in 96 in the placebo group, with a symptom onset of at least 7 days after the second injection, for a vaccine efficacy of 89.7% (95% confidence interval [CI], 80.2 to 94.6). No hospitalizations or deaths were reported among the 10 cases in the vaccine group. Five cases of severe infection were reported, all of which were in the placebo group. A post hoc analysis showed an efficacy of 86.3% (95% CI, 71.3 to 93.5) against the B.1.1.7 (or alpha) variant and 96.4% (95% CI, 73.8 to 99.5) against non-B.1.1.7 variants. Reactogenicity was generally mild and transient. The incidence of serious adverse events was low and similar in the two groups.

CONCLUSIONS

A two-dose regimen of the NVX-CoV2373 vaccine administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection and showed high efficacy against the B.1.1.7 variant. (Funded by Novavax; EudraCT number, 2020-004123-16.)

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More than a year after its emergence as a global pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with more than 177 million cases resulting in more than 3.8 million deaths worldwide as of June 21, 2021.[1] To control this pandemic, efforts were accelerated to develop safe and effective vaccines against SARS-CoV-2 by targeting the spike glycoprotein of the prototype strain.[2] By early 2021, several vaccine candidates had emerged as safe and effective in preventing coronavirus disease 2019 (Covid-19), findings that supported the emergency use of these vaccines around the world.[3-6]

In late 2020, reports from the United Kingdom, Brazil, and South Africa confirmed the emergence of SARS-CoV-2 variants — B.1.1.7 (or alpha), P.1 (or gamma), and B.1.351 (or beta), respectively — that have been associated with increased transmission, more severe disease, and varying degrees of immune avoidance to Covid-19 vaccines.[7-9] In the United Kingdom, the B.1.1.7 variant was identified from genomic sequencing of samples obtained from patients with Covid-19 in the southeast of England in early October 2020. During December 2020, this new variant spread from the southeast region to London and the rest of the country. Subsequently, the prevalence of the B.1.1.7 variant has been increasing rapidly in Europe and the United States.[7] These new variants may threaten our current attempts at controlling Covid-19 and lead to additional health and socioeconomic consequences.

Early clinical data from studies of the NVX-CoV2373 vaccine (Novavax), which consists of 5 μg of a recombinant nanoparticle spike protein plus 50 μg of Matrix-M adjuvant, have shown that a two-dose regimen administered 21 days apart was safe and associated with a robust immune response in healthy adult participants.[10,11] Here, we present data from the 2019nCoV-302 study, a phase 3, randomized, observer-blinded, placebo-controlled trial, to evaluate the efficacy, immunogenicity, and safety of NVX-CoV2373 in preventing Covid-19 in participants between the ages of 18 and 84 years in the United Kingdom. This ongoing trial was initiated during the period in which the B.1.1.7 variant was starting to circulate more widely.

Methods

Trial Design and Participants

From September 28 to November 28, 2020, we enrolled participants at 33 sites in the United Kingdom. Eligible participants were men and nonpregnant women between the ages of 18 and 84 years who were healthy or had stable chronic medical conditions, including human immunodeficiency virus infection (for which they were receiving highly active antiretroviral therapy) and cardiac and respiratory diseases. Key exclusion criteria were a history of documented Covid-19, treatment with immunosuppressive therapy, or a diagnosis of an immunodeficient condition. The protocol containing the statistical analysis plan is available with the full text of this article at NEJM.org. All the participants provided written informed consent.

A Quick Take is available at NEJM.org

Oversight

The trial was designed and funded by Novavax, the manufacturer of NVX-CoV2373. The trial protocol was approved by the North West–Greater Manchester Central Research Ethics Committee. The trial was performed in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. (Details regarding trial oversight are provided in the Supplementary Appendix, available at NEJM.org.) All data were gathered by the non-Novavax authors (representing each trial site) and their teams; all the analyses were performed by representatives of Novavax. Confidentiality agreements were in place between all the authors and the trial sponsor. The first draft of the manuscript was written by the first author with subsequent contributions from all the authors. Editorial assistance in the preparation of the manuscript was provided by Phase Five Communications and funded by Novavax. All trial data were available to all the authors. Safety oversight for specific rules regarding a pause in vaccination was performed by an independent safety monitoring committee. All the authors assume responsibility 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 5-μg doses of NVX-CoV2373 or

placebo (normal saline) administered 21 days apart by means of a centralized interactive-response system, according to a pregenerated randomization schedule. Randomization was stratified according to trial site and age (<65 years or ≥65 years). In a 400-person subgroup, participants received a concomitant dose of seasonal influenza vaccine along with the first dose of NVX-CoV2373. Results of this subgroup analysis, along with immunogenicity data from the current trial, are not reported here.

Because this was an observer-blinded trial, site personnel who were aware of trial-group assignments managed the logistics and preparation of the trial vaccines but were not involved in trial-related assessments and did not have contact with the participants for data collection after vaccine administration.

SAFETY

Safety was assessed in all the participants who had received at least one dose of NVX-CoV2373 or placebo. Solicited local and systemic adverse events were summarized according to the toxicity grading criteria of the Food and Drug Administration (FDA) (Appendix 4 in the protocol) and the time period after each injection. Unsolicited adverse events were coded according to the preferred terms and system organ classes in the *Medical Dictionary for Regulatory Activities*, version 23.1, and summarized according to severity (mild, moderate, or severe) and the assessed relationship to the vaccine. (Details are provided in Section 6.4.1.4 in the protocol.)

After each injection, participants were observed for at least 30 minutes to monitor for any acute reactions. Solicited local and systemic adverse events were collected by means of an electronic diary for 7 days after each dose in a subgroup of participants (solicited adverse event subgroup). All the participants were assessed for unsolicited adverse events from the first dose through 28 days after the second dose. In this ongoing study, we are evaluating serious adverse events, adverse events of special interest, and medically attended adverse events from the first dose through 1 year after the second dose.

EFFICACY

The primary end point was the efficacy of the NVX-CoV2373 vaccine against the first occurrence of virologically confirmed symptomatic mild, moderate, or severe Covid-19 with onset at least 7 days after the second dose among participants who were seronegative at baseline, as determined by the results of testing for anti–nucleocapsid antibody. Symptomatic Covid-19 was defined according to the criteria of the FDA.

The severity of Covid-19 cases was determined in a blinded fashion on the basis of a prespecified, automated algorithm. This algorithm synthesized data points (e.g., symptom diary entries, emergency department and hospitalization records, findings on physical examination, and vital signs) collected throughout the trial to assign severity on the basis of the FDA criteria (Table S1 in the Supplementary Appendix). Symptoms of suspected Covid-19 were monitored throughout the trial and collected with the use of an electronic diary (the InFLUenza Patient-Reported Outcome questionnaire) for at least 10 days. At the onset of suspected symptoms, respiratory specimens from the nose and throat were collected daily over a 3-day period to confirm the presence of SARS-CoV-2 infection, and a clinical assessment was performed. Virologic confirmation was performed by means of polymerase-chain-reaction (PCR) assay at the U.K. Department of Health and Social Care laboratories with the TaqPath system (Thermo Fisher Scientific). Samples were not available for sequencing, and virus-strain characterization was based on PCR data alone.[12] Results were described as being S-gene negative (or having S-gene target failure) if the PCR target of the spike-protein gene was not detected but other PCR targets (i.e., N and ORF1ab genes) were detected; such results were presumed to indicate the presence of B.1.1.7 variants. (Details regarding these analyses are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We determined that the enrollment of approximately 15,000 participants (resulting in a total number of 100 mild, moderate, or severe cases of Covid-19) would provide an overall power of more than 95% to determine a vaccine efficacy of 70% or more. A single interim analysis of efficacy was to be conducted after the identification of approximately 50% of the total anticipated primary end points (50 events) with the use of Pocock stopping boundaries. The main hypothesis-testing, event-driven interim and final analyses of the primary end point were per-

formed at an overall one-sided type I error rate of 0.025 for the primary end point.

The primary end point was analyzed in the per-protocol efficacy population, which consisted of the participants who were seronegative at baseline, had received both doses of trial vaccine or placebo, had no major protocol deviations affecting the primary end point, and had no confirmed cases of symptomatic Covid-19 during the period from the first dose until 6 days after the second dose. We also performed an intention-to-treat analysis, which included all the participants who had undergone randomization and had received at least one dose of vaccine or placebo. Vaccine efficacy was defined as VE (%) = (1 − RR) × 100, in which RR is the relative risk of incidence between the two trial groups. Mean values for disease occurrence are reported as the incidence per year per 1000 participants. The estimated relative risk and its confidence interval were calculated with the use of Poisson regression with robust error variance.[13] Hypothesis testing of the primary end point was performed against the null hypothesis of a vaccine efficacy of 30% or less. The success criterion required rejection of the null hypothesis to show a vaccine efficacy that met the criteria for statistical significance. All other efficacy end points were analyzed by means of the same method that was used for determining the primary efficacy end point without adjustment for multiple comparisons (i.e., at a two-sided alpha of 0.05).

RESULTS

PARTICIPANTS

Of the 16,645 participants who were screened, 15,187 underwent randomization (Fig. 1). A total of 15,139 participants received at least one dose of NVX-CoV2373 (7569 participants) or placebo (7570 participants); 14,039 participants (7020 in the vaccine group and 7019 in the placebo group) met the criteria for the per-protocol efficacy population.

The demographic and clinical characteristics of the participants at baseline were well balanced between the groups in the per-protocol efficacy population, in which 48.4% were women; 94.5% were White, 2.9% were Asian, and 0.4% were Black. A total of 44.6% of the participants had at least one coexisting condition that had been defined by the Centers for Disease Control and Prevention as a risk factor for severe Covid-19. These conditions included chronic respiratory, cardiac, renal, neurologic, hepatic, and immunocompromising conditions as well as obesity.[14] The median age was 56 years, and 27.9% of the participants were 65 years of age or older (Table 1).

SAFETY

A total of 2310 participants were included in the subgroup in which adverse events were solicited. Solicited local adverse events were reported more frequently in the vaccine group than in the placebo group after both the first dose (57.6% vs. 17.9%) and the second dose (79.6% vs. 16.4%) (Fig. 2). Among the vaccine recipients, the most commonly reported local adverse events were injection-site tenderness or pain after both the first dose (with 53.3% reporting tenderness and 29.3% reporting pain) and the second dose (76.4% and 51.2%, respectively), with most events being grade 1 (mild) or 2 (moderate) in severity and of a short mean duration (2.3 days of tenderness and 1.7 days of pain after the first dose and 2.8 and 2.2 days, respectively, after the second dose). Solicited local adverse events were reported more frequently among younger vaccine recipients (18 to 64 years of age) than among older recipients (≥65 years).

Solicited systemic adverse events were reportedly more frequently in the vaccine group than in the placebo group after both the first dose (45.7% vs. 36.3%) and the second dose (64.0% vs. 30.0%) (Fig. 2). Among the vaccine recipients, the most commonly reported systemic adverse events were headache, muscle pain, and fatigue after both the first dose (24.5%, 21.4%, and 19.4%, respectively) and the second dose (40.0%, 40.3%, and 40.3%, respectively), with most events being grade 1 or 2 in severity and of a short mean duration (1.6, 1.6, and 1.8 days, respectively, after the first dose and 2.0, 1.8, and 1.9 days, respectively, after the second dose). Grade 4 systemic adverse events were reported in 3 vaccine recipients. Two participants reported a grade 4 fever (>40 °C), one after the first dose and the other after the second dose. A third participant was found to have had positive results for SARS-CoV-2 on PCR assay at baseline. Five days after dose 1, this participant was hospitalized for Covid-19 symptoms and subsequently had six grade 4 events: nausea, headache,

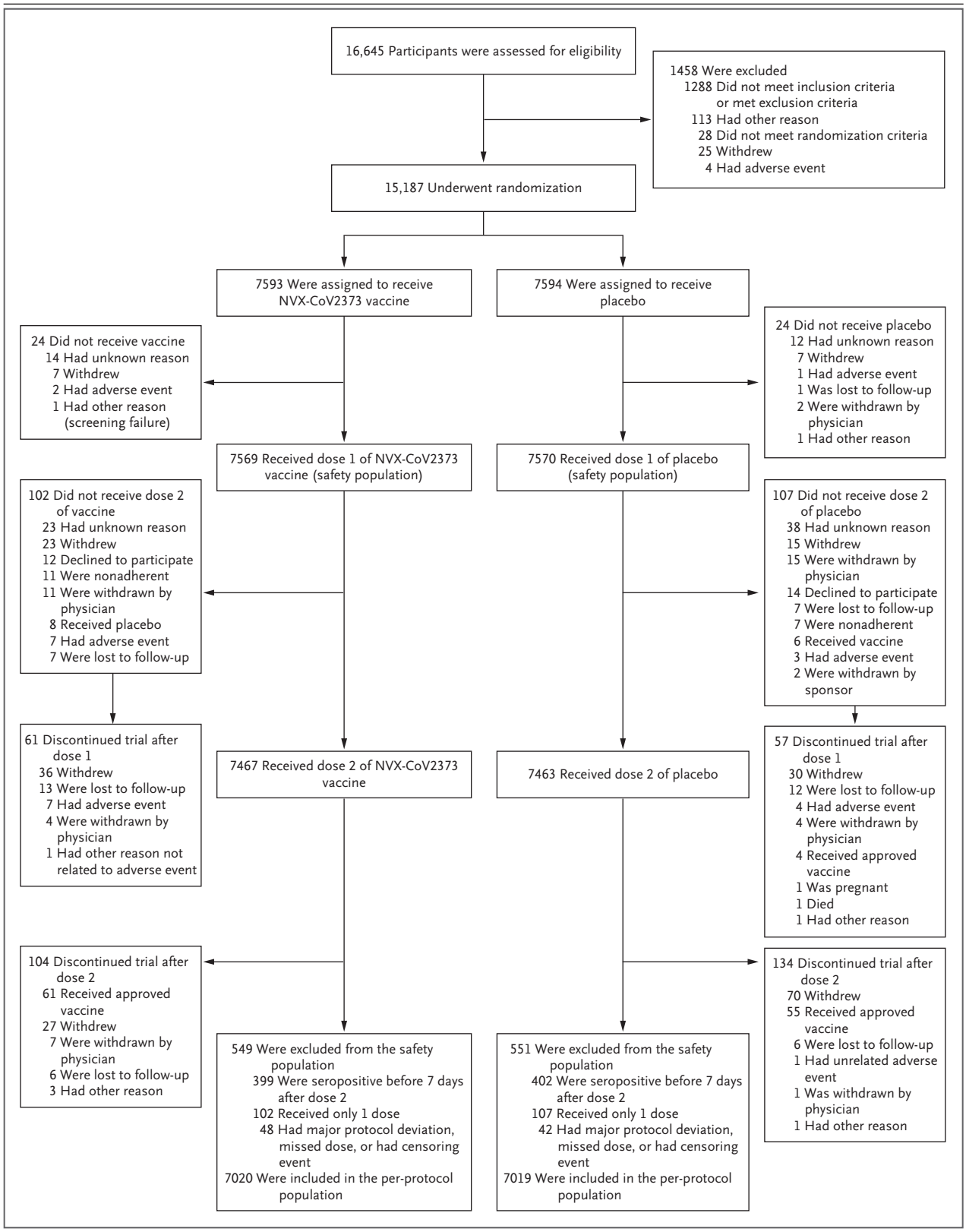


Figure 1 (facing page). Enrollment and Outcomes.
The full analysis set (safety population) included all the participants who had undergone randomization and received at least one dose of the NVX-CoV2373 vaccine or placebo, regardless of protocol violations or missing data. The primary end point was analyzed in the per-protocol population, which included participants who were seronegative at baseline, had received both doses of trial vaccine or placebo, had no major protocol deviations affecting the primary end point, and had no confirmed cases of symptomatic coronavirus disease 2019 (Covid-19) during the period from the first dose until 6 days after the second dose.

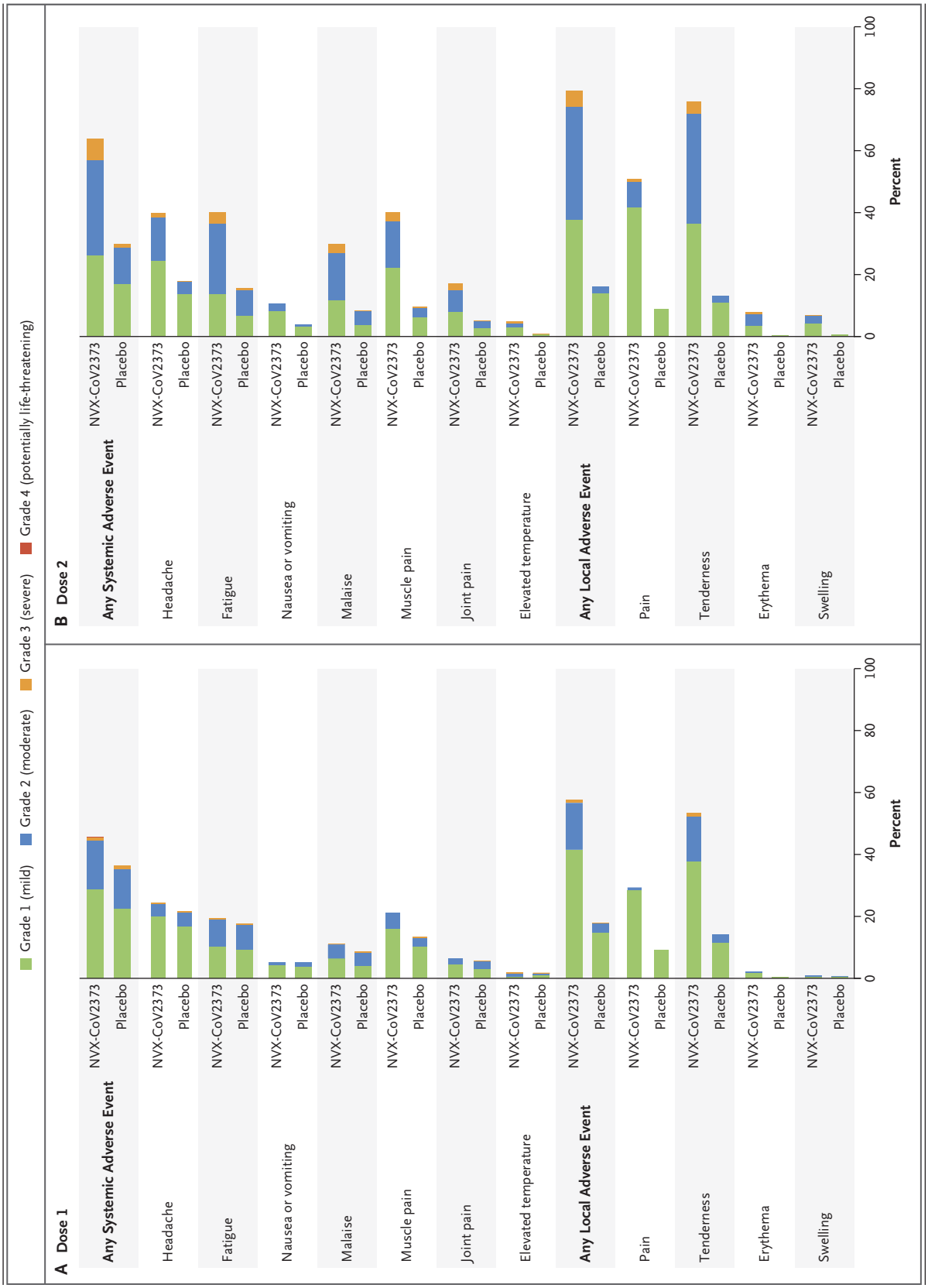
fatigue, myalgia, malaise, and joint pain. Systemic adverse events were reported more often by younger vaccine recipients than by older vaccine recipients and more often after the second dose than after the first dose. Among the vaccine recipients, fever (temperature, ≥38°C) was reported in 2.0% after the first dose and in 4.8% after the second dose. Grade 3 fever (39°C to 40°C) was reported in 0.4% after the first dose and in 0.6% after the second dose; grade 4 fever (>40°C) was reported in 2 participants, with one event after the first dose and one after the second dose.

All 15,139 participants who had received at least one dose of vaccine or placebo through the data cutoff date of the final efficacy analysis were assessed for unsolicited adverse events. The frequency of unsolicited adverse events was higher among vaccine recipients than among placebo recipients (25.3% vs. 20.5%), with similar frequencies of severe adverse events (1.0% vs. 0.8%), serious adverse events (0.5% vs. 0.5%), medically attended adverse events (3.8% vs. 3.9%), adverse events leading to discontinuation of dosing (0.3% vs. 0.3%) or participation in the trial (0.2% vs.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Per-Protocol Efficacy Population).

Characteristic	NVX-CoV2373 (N=7020)	Placebo (N=7019)	All Participants (N=14,039)
Median age (range) — yr	56 (18–84)	56 (18–84)	56 (18–84)
Age group — no. (%)			
18–64 yr	5067 (72.2)	5062 (72.1)	10,129 (72.1)
≥65 yr	1953 (27.8)	1957 (27.9)	3,910 (27.9)
Sex — no. (%)			
Male	3609 (51.4)	3629 (51.7)	7,238 (51.6)
Female	3411 (48.6)	3390 (48.3)	6,801 (48.4)
Race or ethnic group — no. (%)*			
White	6625 (94.4)	6635 (94.5)	13,260 (94.5)
Black	26 (0.4)	26 (0.4)	52 (0.4)
Asian	201 (2.9)	212 (3.0)	413 (2.9)
Hispanic or Latinx	63 (0.9)	51 (0.7)	114 (0.8)
Multiple races	70 (1.0)	59 (0.8)	129 (0.9)
Other	4 (0.1)	6 (0.1)	10 (0.1)
Not reported or missing data	89 (1.3)	81 (1.2)	170 (1.2)
Body-mass index >30 — no. (%)†	1784 (25.4)	1863 (26.5)	3,647 (26.0)
Coexisting condition — no. (%)‡			
Yes	3117 (44.4)	3143 (44.8)	6,260 (44.6)
No	3903 (55.6)	3876 (55.2)	7,779 (55.4)

* Race or ethnic group was reported by the participants, who could have listed more than one category.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. A value of more than 30 is considered to indicate obesity.
‡ Coexisting conditions that were classified by the Centers for Disease Control and Prevention as risk factors for severe Covid-19 included chronic respiratory, cardiac, renal, neurologic, hepatic, and immunocompromising conditions as well as obesity.



0.2%), potential immune-mediated medical conditions (<0.1% vs. <0.1%), and adverse events of special interest relevant to Covid-19 (0.1% vs. 0.3%). One related serious adverse event (myocarditis) was reported in a vaccine recipient, which occurred 3 days after the second dose and was considered to be a potentially immune-mediated condition; an independent safety monitoring committee considered the event most likely to be viral myocarditis. The participant had a full recovery after 2 days of hospitalization. No episodes of anaphylaxis or vaccine-associated enhanced Covid-19 were reported.

Two deaths related to Covid-19 were reported, one in the vaccine group and one in the placebo group. The death in the vaccine group occurred in a 53-year-old man in whom Covid-19 symptoms developed 7 days after the first dose; he was subsequently admitted to the ICU for treatment of respiratory failure from Covid-19 pneumonia and died 15 days after vaccine administration. The death in the placebo group occurred in a 61-year-old man who was hospitalized 24 days after the first dose; the participant died 4 weeks later after complications from Covid-19 pneumonia and sepsis.

EFFICACY

Among the 14,039 participants in the per-protocol efficacy population, cases of virologically confirmed, symptomatic mild, moderate, or severe Covid-19 with an onset at least 7 days after the second dose occurred in 10 vaccine recipients (6.53 per 1000 person-years; 95% confidence interval [CI], 3.32 to 12.85) and in 96 placebo recipients (63.43 per 1000 person-years; 95% CI, 45.19 to 89.03), for a vaccine efficacy of 89.7% (95% CI, 80.2 to 94.6) (Fig. 3). Of the 10 vaccine breakthrough cases, 8 were caused by the B.1.1.7 variant, 1 was caused by a non-B.1.1.7 variant, and 1 viral strain could not be identified. Ten cases of mild, moderate, or severe Covid-19 (1 in the vaccine group and 9 in the placebo group) were reported in participants who were 65 years of age or older (Fig. 4). Severe Covid-19 occurred in 5 participants, all in the placebo group. Among these cases, 1 patient was hospitalized and 3 visited the emergency department; a fifth participant was cared for at home. All 5 patients met additional criteria regarding abnormal vital signs, use of supplemental oxygen, and Covid-19 complications that were used to define severity (Table S1). No hospitalizations or deaths from Covid-19 occurred among the vaccine recipients in the per-protocol efficacy analysis.

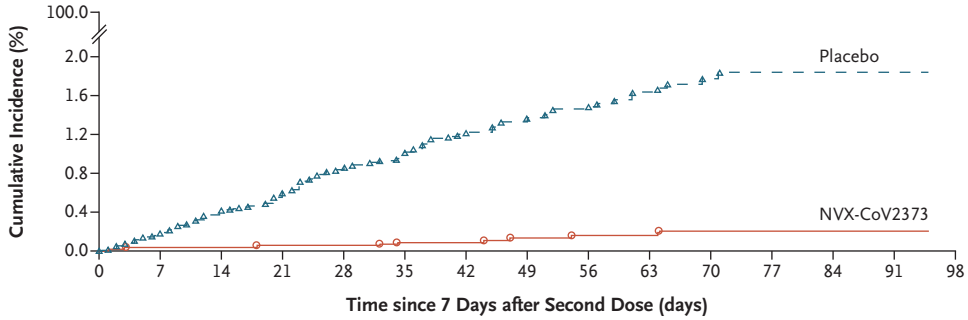
Additional efficacy analyses in subgroups (defined according to age, race, and presence or absence of coexisting conditions) are detailed in Figure 4. Among the participants who were 65 years of age or older, overall vaccine efficacy was 88.9% (95% CI, 12.8 to 98.6); efficacy among all the participants starting 14 days after the first dose was 83.4% (95% CI, 73.6 to 89.5). A post hoc analysis of the primary end point identified the B.1.1.7 variant in 66 participants and a non-B.1.1.7 variant in 29 participants; in 11 participants, PCR testing had been performed at a local hospital laboratory in which the variant had not been identified. Vaccine efficacy was 86.3% (95% CI, 71.3 to 93.5) against the B.1.1.7 variant and 96.4% (95% CI, 73.8 to 99.4) against non-B.1.1.7 strains. Too few non-White participants were enrolled in the trial to draw meaningful conclusions about variations in efficacy on the basis of race or ethnic group.

DISCUSSION

A two-dose regimen of the NVX-CoV2373 vaccine administered 21 days apart was found to be safe and 89.7% effective against symptomatic Covid-19 caused by both B.1.1.7 and non-B.1.1.7 variants. The timing of accumulated cases in this trial allowed for a post hoc assessment of vaccine efficacy against strains that included the B.1.1.7 variant, which is now circulating widely outside the United Kingdom and was the most widespread strain reported in the United States at the time of this report[15] (Table S5). This variant is known to be more transmissible and to be associ-

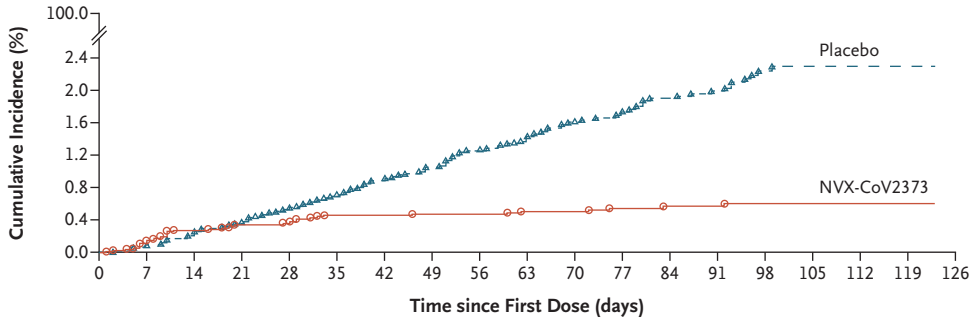
Figure 2 (facing page). Solicited Local and Systemic Adverse Events.
The percentage of participants who had solicited local and systemic adverse events during the 7 days after each injection of the NVX-CoV2373 vaccine or placebo is plotted according to the maximum toxicity grade (mild, moderate, severe, or potentially life-threatening). Data are not included for the 400 trial participants who were also enrolled in the seasonal influenza vaccine substudy.

A Per-Protocol Population



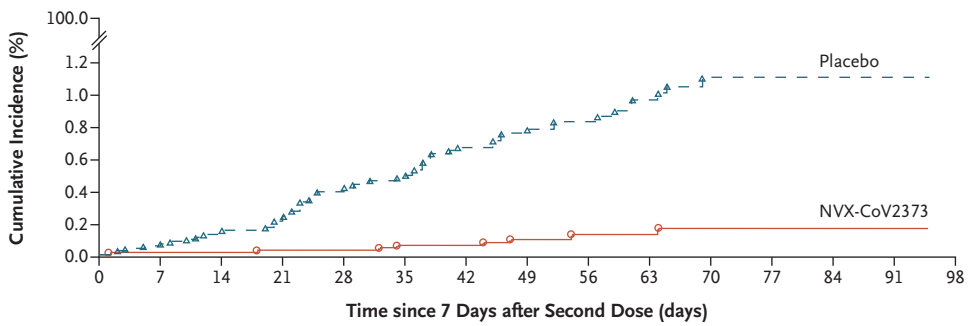
No. at Risk															
Placebo	7019	6978	6896	6777	6617	6260	5199	4269	3388	2629	1758	862	230	10	0
NVX-CoV2373	7020	6989	6930	6847	6689	6343	5297	4342	3421	2664	1790	896	251	11	0
No. with Event															
Placebo	1	13	28	40	57	66	77	84	88	92	95	96	96	96	96
NVX-CoV2373	0	3	3	4	4	6	6	8	9	9	10	10	10	10	10

B Intention-to-Treat Population



No. at Risk																			
Placebo	7565	7554	7540	7520	7475	7425	7342	7238	7089	6808	5661	4658	3761	2906	1995	1017	317	12	0
NVX-CoV2373	7566	7555	7541	7526	7483	7440	7385	7304	7148	6893	5760	4739	3821	2973	2058	1058	334	13	0
No. with Event																			
Placebo	0	7	20	29	42	54	69	79	95	106	118	124	131	134	140	141	141	141	141
NVX-CoV2373	0	11	21	26	29	35	35	36	36	38	38	40	41	41	42	42	42	42	42

C Participants with B.1.1.7 Variant in the Per-Protocol Population



No. at Risk															
Placebo	7019	6985	6912	6799	6645	6288	5228	4292	3408	2644	1769	868	233	11	0
NVX-CoV2373	7020	6991	6932	6848	6690	6344	5298	4343	3422	2664	1790	896	251	11	0
No. with Event															
Placebo	0	5	11	17	29	34	44	49	51	55	58	58	58	58	58
NVX-CoV2373	0	1	1	2	2	4	4	6	7	7	8	8	8	8	8

Figure 3 (facing page). Kaplan–Meier Plots of Efficacy of the NVX-CoV2373 Vaccine against Symptomatic Covid-19.
Shown is the cumulative incidence of symptomatic Covid-19 in the per-protocol population (Panel A), the intention-to-treat population (Panel B), and the per-protocol population with the B.1.1.7 variant (Panel C). The timing of surveillance for symptomatic Covid-19 began after the first dose in the intention-to-treat population and at least 7 days after the administration of the second dose in the per-protocol population (i.e., on day 28) through approximately the first 3 months of follow-up.

ated with a higher case fatality rate than previous strains.[7] Vaccine efficacy was greater than that associated with the ChAdOx1 nCoV-19 vaccine (AstraZeneca) (70.4%) in a smaller phase 2–3 trial.[16]

Although the trial was not powered to assess efficacy for all the circulating SARS-CoV-2 strains, it is reassuring that substantial efficacy was shown against all the strains that were detected in the trial participants. In particular, the efficacy estimate of 96.4% against the non-B.1.1.7 strains (the majority of which were the prototype strain[17]) is similar to the efficacy of 95.0% reported against this strain for the BNT161b2 messenger RNA (mRNA) vaccine (BioNTech/Pfizer) and the efficacy of 94.1% for the mRNA-1273 vaccine (Moderna).[3,4] The vaccine efficacy was also greater than that reported for the adenoviral vector vaccines.[5,6] Finally, as assessed elsewhere,[18] the NVX-CoV2373 vaccine has also shown efficacy against the B.1.351 variant, albeit at a lower level (51.0%) than has been shown for the B.1.1.7 and non-B.1.1.7 strains.

Prevention of severe disease (including hospitalization, intensive care admission, and death) is an important objective of a vaccination program, and the two-dose regimen of the NVX-CoV2373 vaccine showed very high efficacy against this end point, similar to that reported for other licensed Covid-19 vaccines.[3-6] In addition, although this trial was not designed to assess vaccine efficacy after a single dose, NVX-CoV2373 provided levels of protection after the first dose in a range similar to those of other Covid-19 vaccines.[3-6] The favorable safety profile that was observed during phase 1–2 studies of NVX-CoV2373 was confirmed in this phase 3 trial. Reactogenicity was generally mild or moderate, and reactions were less common and milder in older participants and more common after the second dose.

Subgroup	Placebo	NVX-CoV2373	Vaccine Efficacy (95% CI)
	no. of events/no. at risk		%
Per-protocol population	96/7019	10/7020	89.7 (80.2 to 94.6)
Intention-to-treat population	141/7570	42/7569	70.4 (58.3 to 79.1)
Age			
18 to <65 yr	87/5062	9/5067	89.8 (79.7 to 95.5)
≥65 to 84 yr	9/1957	1/1953	88.9 (20.2 to 99.7)
Race			
White	85/6635	8/6625	90.7 (80.8 to 96.1)
Other	8/297	2/302	75.7 (–21.6 to 97.5)
Variant			
Non-B.1.1.7	28/7020	1/7020	96.4 (73.8 to 99.5)
B.1.1.7	58/7020	8/7020	86.3 (71.3 to 93.5)
Coexisting illness			
Yes	33/3143	3/3117	90.9 (70.4 to 97.2)
No	63/3876	7/3903	89.1 (76.2 to 95.0)

Figure 4. Vaccine Efficacy of NVX-CoV2373 in Specific Subgroups.
Shown is the efficacy of the NVX-CoV2373 vaccine in preventing Covid-19 in various subgroups within the per-protocol population. Vaccine efficacy and 95% confidence intervals were derived with the use of Poisson regression with robust error variance. In the intention-to-treat population, vaccine efficacy was assessed after the administration of the first dose of vaccine or placebo. Participants who identified themselves as being non-White or belonging to multiple races were pooled in a category of "other" race to ensure that the subpopulations would be large enough for meaningful analyses. Data regarding coexisting conditions were based on the definition used by the Centers for Disease Control and Prevention for persons who are at increased risk for Covid-19.

Injection-site tenderness and pain, fatigue, headache, and muscle pain were the most commonly reported local and systemic adverse events. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.5% in each), and no deaths were attributed to the receipt of the vaccine.

This trial has several limitations. Although approximately 7500 participants received NVX-CoV2373, it is not possible to exclude the occurrence of rare adverse events. However, such events may be captured through the ongoing follow-up of participants, which is planned to continue until 12 months after the administration of the second dose of vaccine and is also being assessed in the larger PREVENT-19 phase 3 trial (ClinicalTrials.gov number, NCT04611802). The PREVENT-19 trial was also able to enroll a larger number of participants in racial and ethnic minority groups, whereas only 5.7% of participants in the current trial were non-White. Similarly, the efficacy estimates reported here are derived from a relatively short duration of observation (median, 3 months after dose 2). Thus, the ongoing follow-up will provide data regarding the durability of vaccine efficacy, a continued assessment of severe cases, and an assessment of efficacy against asymptomatic disease. A further limitation of the current trial is the lack of sequencing data on viral isolates, although the use of S-gene target failure, as detected by the TaqPath assay, has proved to be a reliable proxy for the presence of B.1.1.7 variants.

The results of this trial provide further evidence that immunization with a protein-based, adjuvanted vaccine such as NVX-CoV2373 can prevent Covid-19 caused by either B.1.1.7 or non-B.1.1.7 variants. In addition, NVX-CoV2373 can be stored at standard refrigeration temperatures and has the potential to induce a broad epitope response to the spike protein antigen. Both of these attributes are important for the efficient implementation of this vaccine globally in view of the continued need to vaccinate against emerging variants.

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APPENDIX

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