Safety and Efficacy of the NVX-CoV2373 COVID-19 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial

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ABSTRACT

Background. The recombinant protein-based vaccine, NVX-CoV2373, demonstrated 89.7% efficacy against COVID-19 in a phase 3, randomized, observer-blinded, placebo-controlled trial in the United Kingdom. The protocol was amended to include a blinded crossover; data to the end of the placebo-controlled phase are reported.

Methods. Adults aged 18–84 years received two doses of NVX-CoV2373 or placebo (1:1) and were monitored for virologically confirmed mild, moderate, or severe COVID-19 (onset from 7 days after second vaccination). Participants who seroconverted to immunoglobulin G (IgG) against the nucleocapsid protein and did not meet criteria for symptomatic COVID-19 were classified as having asymptomatic disease. Secondary outcomes included anti-spike (S) IgG responses, wild-type virus neutralization, and T-cell responses.

Results. Of 15185 participants, 13989 remained in the per-protocol efficacy population (6989 NVX-CoV2373, 7000 placebo). At a maximum of 7.5 months (median, 4.5 months) postvaccination, there were 24 cases of COVID-19 among NVX-CoV2373 recipients and 134 cases among placebo recipients, a vaccine efficacy of 82.7% (95% CI: 73.3–88.8). Vaccine efficacy was 100% (17.9–100.0) against severe disease and 76.3% (57.4–86.8) against asymptomatic disease. High anti-S and neutralization responses to vaccination were evident, together with S-protein–specific induction of interferon-γ secretion in peripheral blood T cells. Incidence of serious adverse events and adverse events of special interest were similar between groups.

Conclusions. A two-dose regimen of NVX-CoV2373 conferred a high level of ongoing protection against asymptomatic, symptomatic, and severe COVID-19 through >6 months postvaccination. A gradual decrease of protection suggests that a booster dose may be indicated.

Keywords. COVID-19; immunogenicity; asymptomatic infection; SARS-CoV-2; vaccine efficacy.

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide, with 608 million cases and 6.5 million deaths reported as of 16 September 2022 [1].

Vaccination remains one of the key elements for pandemic control. International efforts have led to development of safe and effective COVID-19 vaccines targeting the virus spike (S) glycoprotein, with 38 vaccine candidates currently in clinical use [2].

Efforts to control the COVID-19 pandemic have been hindered by emergence of several SARS-CoV-2 genotypic variants, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). These viral strains have shown increased transmissibility, severity of clinical disease, and potential immunologic escape from COVID-19 vaccine protection [3–7]. The Alpha variant was the most prevalent strain in the United Kingdom between January and May 2021 but was gradually replaced by the Delta variant, reaching 90% of sequenced cases by June 2021 [8]. Delta was rapidly replaced by the Omicron variant from November 2021 [9, 10]. In this context of emerging variants, it is crucial to closely monitor longer-term vaccine efficacy.

Effectiveness of COVID-19 vaccines in preventing asymptomatic infection is also important when considering the overall impact of vaccine programs. Prevention of both symptomatic and asymptomatic infection is likely to have a larger impact on interrupting transmission than prevention of symptomatic disease alone. Currently, limited data are available on vaccine efficacy against asymptomatic disease from randomized trials; 63% efficacy was reported for the mRNA-1273 vaccine (compared with 93.2% against symptomatic illness) [11], 28.9% for the Ad26.COV2.S vaccine [12], and 22.2% to 49.3% (depending on vaccine dose and schedule) for the ChAdOx1 nCoV-19 vaccine [13].

The NVX-CoV2373 vaccine is a recombinant, nanoparticle, S protein with a Matrix-M™ adjuvant. Two 5-µg doses of vaccine, administered 21 days apart, have demonstrated safety and immunogenicity in phase 1/2 trials [14, 15] and high efficacy in two phase 3 trials [16, 17]. The 2019nCoV-302 study is a phase 3, randomized, observer-blinded, placebo-controlled trial evaluating efficacy, immunogenicity, and safety of the NVX-CoV2373 vaccine in preventing COVID-19 in adults aged 18–84 years in the United Kingdom. We previously reported 89.7% protection against all symptomatic SARS-CoV-2 infection in the primary event-driven analysis, including high efficacy against the Alpha variant [18] and 96.4% efficacy against non-Alpha strains. The trial included a planned blinded crossover, ending the placebo-controlled portion of the study (conducted from 29 March to 14 June 2021). The current report provides study results for safety and efficacy through to the end of the placebo-controlled period and previously unreported immunogenicity analyses.

METHODS

Trial Design and Participants

The methodology and full protocol for this trial have been previously published [16]. Briefly, we assessed safety and efficacy of two 5-µg doses of NVX-CoV2373 or placebo, administered intramuscularly 21 days apart. This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 33 sites across the United Kingdom. Eligible participants were men and non-pregnant women aged 18 to 84 years (inclusive) who were healthy or had stable chronic medical conditions including, but not limited to, HIV (receiving effective antiretroviral therapy), cardiac, and respiratory diseases. Participants were randomly (1:1) assigned via block randomization to receive two doses of NVX-CoV2373 or placebo (normal saline) using a

centralized Interactive Response Technology system according to pre-generated randomization schedules. Randomization was stratified by site and by age ≥ 65 years. Key exclusion criteria included history of documented COVID-19 and treatment with immunosuppressive therapy.

Results from the planned primary event-driven analysis, which included a median of approximately 3 months of follow up (data cutoff date: 29 January 2021), have been published [16]. The protocol was amended on 25 February 2021 to include a blinded crossover phase in which subsequent doses of study vaccine were administered from 29 March to 14 June 2021, so all participants could receive active vaccine during the study. Participants could request to be unblinded at any time during the study, whereby they could choose to receive an authorized COVID-19 vaccine through the UK National Health Service (NHS), remain in the study for safety follow-up, or withdraw from the study entirely. Those who remained blinded entered the blinded crossover or chose to remain blinded and not enter the blinded crossover (**Figure 1**). For this analysis, safety and efficacy data from this ongoing phase 3 trial were assessed at a maximum of 7.5 months (median 4.5 months) after study start.

The trial protocol was approved by the North West—Greater Manchester Central Research Ethics Committee (Ref 20/NW/03/99) and was performed in accordance with the International Council for Harmonization Good Clinical Practice guidelines. Safety oversight was performed by an independent safety monitoring committee.

Safety

Safety data are reported for all participants who received at least one dose of vaccine or placebo. This includes serious adverse events (SAEs), AEs of special interest (AESIs), and related

medically attended AEs (MAAEs) through to the end of the placebo-controlled period (**Supplementary Tables S1 and S2**).

Efficacy

Efficacy was assessed as per previously-reported methods [16]. Symptomatic COVID-19 was defined according to US Food and Drug Administration (FDA) criteria [19]. Symptoms of suspected COVID-19 were monitored throughout the trial and collected using an electronic symptom diary for at least 10 days after symptom start date. Virological confirmation was performed using polymerase chain reaction (PCR) testing. Asymptomatic infection was defined as occurring in participants with a positive PCR test result for SARS-CoV-2 or who seroconverted after Day 35 (2 weeks after second vaccination) to immunoglobulin G (IgG) against the nucleocapsid protein (N-protein), without any symptoms or with symptoms that did not meet the symptomatic endpoint criteria (see protocol for details) **(Supplementary Methods)**. An additional efficacy endpoint included the first occurrence of laboratory-confirmed (by PCR or N-protein serology test) symptomatic or asymptomatic COVID-19 with onset at least 7 days after second study vaccination in participants with negative serostatus at baseline.

Immunogenicity Assessments

Detection of SARS-CoV-2 anti–N-protein IgG (Roche Elecsys Anti-SARS-CoV-2, Indianapolis, IN) was performed at baseline, Day 35, 3 months, and just before receiving a crossover dose in all participants to establish serostatus and for assessment of asymptomatic disease. An enzyme-linked immunosorbent assay (ELISA) for SARS-CoV-2 anti-S protein IgG (Novavax, Gaithersburg, MD) and a microneutralization assay (360 bioLabs, Melbourne, Australia) were

performed at baseline and on Day 35 in approximately 900 consecutive participants from 2 study sites (immunogenicity cohort). Induction of S-protein–specific T-cell responses by immunization was measured at baseline and on Day 35 in approximately 450 consecutive participants from 2 study sites using ELISpot assays to detect T cells in peripheral blood responsive to SARS-CoV-2 S-protein peptides (Oxford Immunotech) (Assays are detailed in the **Supplementary Methods**).

Statistical Analysis

Safety analysis

Safety events were summarized descriptively. AEs were coded by preferred term and system organ class using Version 23.1 of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by severity and relationship to study vaccine.

For participants who enrolled in the blinded crossover, safety data were censored at the time of crossover (eg, the date at which participants received their third study dose). For participants who did not enter the blinded crossover and were unblinded (but did not withdraw from the study), safety data were censored at the time of unblinding or the time of receipt of another COVID-19 vaccine (whichever date was noted first). For participants who neither entered the blinded crossover nor were censored, the safety data cutoff date was 27 July 2021 (**Figure 1**).

Efficacy analysis

Efficacy for the current analyses were conducted in the same manner as previously described [16] and detailed in the **Supplementary Methods**. Participants were censored at the

earliest of the date of unblinding (for any reason), date of receipt of another COVID-19 vaccine, date of entering the blinded crossover, date of early withdrawal, date of death, or the cutoff date of 27 July 2021.

Immunogenicity analysis

For the SARS-CoV-2 anti–S-protein IgG antibody levels measured by ELISA, geometric mean at each study visit (baseline and Day 35), the geometric mean fold-rises (GMFRs) comparing Day 0 (baseline) to Day 35, along with 95% CI, were summarized. The 95% CI was calculated based on the t-distribution of the log-transformed values for geometric means or GMFRs, then back-transformed to the original scale for presentation. The seroconversion rate (SCR), proportion of participants with ≥ 4-fold rises if seronegative at baseline, along with 95% CIs based on the Clopper-Pearson method, are summarized by vaccine group. A similar statistical analysis was performed for the microneutralization assay.

T-cell responses to SARS-CoV-2 protein peptide pools were assessed based on counts of cells secreting interferon-gamma (IFN-γ) per 2.5×10^5 peripheral blood mononuclear cells (Oxford Immunotec, Abingdon, Oxfordshire, UK) before immunization (Day 0) and at Day 35. Mean spot counts (with standard deviations) were calculated by treatment group, age stratum, stimulation condition, and timepoint. In addition, GMFRs from baseline by treatment group and age stratum were calculated from within-participant ratios of Day 35 to Day 0 counts.

RESULTS

Participants

Between 28 September and 28 November 2020, a total of 16,631 participants were screened and 15,185 participants were randomized (**Figure 1**). A total of 15,138 participants received at least one dose of NVX-CoV2373 (7569) or placebo (7569). The protocol-specified number of events for the primary event-driven analysis was reached just before the data cutoff date of 29 January 2021 and vaccine efficacy and safety have been reported [16].

The current analysis contains 158 participants who met the primary endpoint definition (24 in vaccine arm and 134 in the placebo arm), occurring between 10 November 2020 and 10 May 2021. The current analysis had a maximum observation period of 7.5 months (28 September 2020 through 10 May 2021) with a median of 4.5 months. Baseline demographics for per-protocol populations are listed in **Table 1**. Baseline participant demographics for the immunogenicity and cell-mediated immunity (CMI) cohorts are listed in the **Supplementary Table S3**.

Safety

All 15,138 participants who received at least one dose of vaccine or placebo were assessed for safety events. NVX-CoV2373 recipients reported higher frequencies of solicited local and systemic AEs than placebo recipients after both the first dose and the second dose, with most events being mild to moderate in severity and of short mean duration [16]. The frequency of unsolicited AEs was higher among NVX-CoV2373 recipients than among placebo recipients (27.4% vs 21.8%), with similar frequencies of severe AEs, SAEs, MAAEs, AEs leading to dose

or study discontinuation, potential immune-mediated medical conditions, and AESIs relevant to COVID-19 (**Table 2**, **Supplementary Table S4**).

There were no episodes of anaphylaxis, thrombosis with thrombocytopenia syndrome or evidence of vaccine-associated enhanced COVID-19. There was one episode of myocarditis previously reported [16] and no cases of pericarditis. By the end of the placebo-controlled phase, there were 7 deaths (NVX-Co2373, n=4; placebo, n=3), none of which were considered related to study vaccine.

Efficacy

Among 13,831 participants in the per-protocol efficacy population before the blinded crossover, there were 24 cases of virologically (PCR) confirmed, symptomatic mild, moderate, or severe COVID-19 with onset at least 7 days after the second dose among vaccine recipients (9.48 per 1000 person-years; 95% CI: 5.82–15.42) and 134 cases among placebo recipients (54.85 per 1000 person-years; 95% CI: 41.03–73.32) for a vaccine efficacy of 82.7% (95% CI: 73.3–88.8). Vaccine efficacy against moderate or severe disease was 79.2% (95% CI: 66.7–87.0), and efficacy against severe COVID-19 was 100% (95% CI: 17.9–100.0); all 6 participants with severe COVID-19 had received placebo (**Figure 2**).

Additional efficacy analyses (among subgroups defined by age, race, sex, presence of comorbid conditions, influenza vaccine co-administration, and disease severity) are detailed in **Figure 3**.

A total of 70 participants (NVX-CoV2373, n=14; placebo, n=56) were found to have asymptomatic infection, a vaccine efficacy of 76.3% (95% CI: 57.4–86.8). Finally, 231

participants (NVX-CoV2373, n=36; placebo, n=195) had either symptomatic or asymptomatic infection, a vaccine efficacy of 82.5% (95% CI: 75.0–87.7).

Immunogenicity

The per-protocol anti–S-protein serology subset was composed of 831 participants (NVX-CoV2373, n=414; placebo, n=417), and the per-protocol neutralization assay subset included 761 participants (NVX-CoV2373, n=381; placebo, n=380). The immunology sets were well balanced between the two vaccine study groups (**Supplementary Tables S5–11**).

Serum anti–S-protein IgG levels in participants at Day 35 were increased relative to placebo across all age groups (**Supplementary Table S5** and **Figures S1–4**). Serum anti–S-protein IgG geometric mean ELISA Units (EU)/mL (GMCs) in the NVX-CoV2373 group were highest in the younger vs older age cohort (18–64 years: 47,564.3 EU/mL; 65–84 years: 37,892.8 EU/mL). Similar differences in responses were observed regardless of baseline serostatus (**Supplementary Tables S5–7**). Serum anti–S-protein IgG GMCs in the NVX-CoV2373 group were highest in the seropositive cohort (125,489.8 EU/mL) vs the seronegative cohort (44,229.9 EU/mL) (**Supplementary Table S7**). These responses equated to serum anti–S-protein IgG GMFRs relative to baseline of 73.9 and 394.3, respectively. SCRs were markedly increased relative to placebo across all baseline serostatus groups (98.9% for all participants; 95.7% seropositive and 99.1% seronegative) and regardless of age group (18–64 years: 99.0%; 65–84 years: 99.1%).

A similar pattern was observed with neutralizing antibody responses, with the highest responses seen in the younger age cohort (**Supplementary Tables S8–10** and **Figures S5–11**) and in those who were seropositive at baseline (**Supplementary Table S10** and **Figure S11**).

T-Cell Responses

ELISpot assays were performed on peripheral blood from 407 per-protocol participants (**Supplementary Table S11, Supplementary Figure S12**). In the NVX-CoV2373 group, strong induction of T cells secreting IFN-γ occurred in response to peptide pools reflecting the full length of the SARS-CoV-2 S-protein, and to its N-terminal and C-terminal portions, with GMFRs of 16.5-, 14.2-, and 8.4-fold, respectively. C-terminal sequences elicited somewhat lesser responses than the full-length or N-terminal peptide pools but with a similar pattern. The amplitude of T-cell responses was generally lower in vaccinated participants aged ≥ 65 years.

DISCUSSION

The data through to the completion of the placebo-controlled stage of this phase 3 trial provide further evidence of the safety and efficacy of NVX-CoV2373 in preventing symptomatic COVID-19. These findings are based on >6 months (median of 4.5 months) of follow-up and are similar to those observed previously at a median follow-up of 3 months [16], indicating only a small reduction in NVX-CoV2373 vaccine efficacy. Of note, NVX-CoV2373 provided substantial protection from laboratory-confirmed asymptomatic infection (76.3%; 95% CI: 57.4–86.8), higher than that reported from randomized controlled trials of other COVID-19 vaccines [11–13] and provided a combined vaccine efficacy of 82.5% (95% CI: 75.0–87.7) against laboratory-confirmed symptomatic or asymptomatic infection. Prevention of both symptomatic and asymptomatic infection is of paramount importance for interrupting viral transmission.

A two-dose regimen of NVX-CoV2373, administered 21 days apart, markedly increased anti–S-protein IgG and neutralizing antibody levels, regardless of baseline serostatus, with higher levels in the younger vs older adult cohort and in those who were seropositive at baseline.

Similar differences in responses related to age and prior exposure have been described for other COVID-19 vaccines and are consistent with immunosenescence and priming, respectively [20, 21]. There was a high correlation between "binding" antibodies (anti–S-protein IgG) and neutralizing antibodies, indicating that the anti–S-protein immunity was predominantly functional. Additionally, evaluation of T-cell responses demonstrates induction of a T-cell population that secretes IFN-γ in response to epitopes within the SARS-CoV-2 S-protein.

The small reduction in vaccine efficacy over time may relate to a decrease in neutralizing antibody titers, as reported for this [22] and other COVID-19 vaccines [23, 24]. To maintain high levels of efficacy, especially for those populations with the greatest susceptibility to severe disease, a booster dose may be warranted. Booster vaccines are most likely to be of greatest importance for those aged ≥65 years who exhibited lower titers and a more significant decrease in vaccine efficacy than those aged <65 years. In another study, a single dose of NVX-CoV2373 administered at 6 months after primary vaccination with 2 doses of NVX-CoV2373 resulted in a marked increase in titers against the prototype strain and all variants evaluated, notably greater than those titers associated with the high levels of efficacy in phase 3 studies of this vaccine [22]. A separate study found significantly improved neutralization of SARS-CoV-2 variants Omicron BA.1 (35-fold increase; $p<0.001$) and BA.4/BA.5 (12-fold increase; $p<0.001$) after a third (booster) dose of NVX-CoV2373 [25]. A study with NVX-CoV2373 administered after a primary series of either the ChAdOx1nCoV-19 or BNT162b2 vaccines showed boosted antibody and neutralizing responses with low levels of reactogenicity [26]. Additional homologous and heterologous studies of NVX-CoV2373 as a booster dose are underway in different populations [6, 17, 22, 26, 27].

The favorable safety profile observed earlier in this study was found to be consistent through to the end of the placebo-controlled period. The incidence of SAEs was similar in the vaccine and placebo groups, and no deaths were attributable to receipt of the vaccine. To date the findings of this and other studies assessing the safety of NVX-CoV2373 [6, 16, 17] have shown no evidence of increased risk for myocarditis/pericarditis or thrombocytopenic-thrombotic events.

This trial has several limitations. The overall duration of the placebo-controlled period was short but necessary to offer study participants the option of receiving the active vaccine. Sequencing data on study isolates were not available, although contemporary data from national surveillance shows the dominance of the Alpha variant during the study period together with the emergence of the Delta variant (**Figure 4**) [28]. As both variants have shown lower vaccine efficacy point estimates with NVX-CoV2373 than against the earlier Wuhan strain [16, 17, 29], this shifting variant landscape, along with the additional time since vaccination, may have contributed to a decrease in vaccine efficacy.

The results of this trial provide further evidence that symptomatic, asymptomatic, and severe SARS-CoV-2 infections can be prevented by a protein-based, adjuvanted vaccine within a maximal period of 7·5 months. NVX-CoV2373 has received conditional authorization in several locations, and this will allow for the accumulation of real-world evidence to further assess vaccine effectiveness, safety, and duration of protection.

NOTES

Contributors

PTH is the chief investigator. PTH, ST, GG, IC, AR contributed to the protocol and design of the study. ST and PTH contributed to the design and execution of the study, the analysis and interpretation of the data, and the writing, reviewing, and editing of text and figures. EPG, DNB, MB, DB, FB, DRC, RC, CAC, JG, ALG, AHe, AHi, SI, CJ, PAK, CK, JMB, CM, AMM, FM, PM, IMu, HN, OO, JP, CHP, ASFR, DS, RPS, RS, RLS, PAS, ECT, JT and MEV are study site principal investigators and contributed to the study data collection. IC and AR conducted the statistical analysis. All authors reviewed, commented on and approved this manuscript before submission for publication.

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Data sharing

The trial protocol and statistical analysis plan have been made available as part of the peer-review process and will be made available upon publishing of the manuscript by request to the corresponding author. Additional information is available at clinicaltrialsregister.eu (EudraCT number, 2020-004123-16).

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Declaration of interests

KA, IC, LF, GG, IMc, EJR, AR, KS, ST are employees of Novavax Inc and as such receive a salary for their work. KS also reports stock received as part of employment compensation from Novavax. AR also reports stock or stock options from Novavax. EJR also reports Novavax stock. KA also reports vested and unvested Novavax stock/RSU. IC also reports stock and stock options and salary and bonus. LF reports consulting fees as a prior full-time employee, now contractor to Novavax re-imbursed hourly for work performed on this study and in analyses and drafting this report, and shares and stock options from Novavax. GG reports stock related compensations from Novavax. IC also reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events as an employee of Novavax and has Novavax stock. ST reports royalties or licenses, salary and stock, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid, all as an employee of Novavax. Guy's and St Thomas' NHS Foundation Trust received funding from Novavax for this trial. ALG received no personal funds from Novavax for this work; funding was awarded to ALG's organization (Guy's and St Thomas' NHS Foundation Trust)

from novavax to deliver this trial. Oxford University has entered into a partnership with Astra Zeneca for further development of ChAdOx1 nCoV-19. Anna Goodman (ALG) is named as an inventor on a patent covering use of a particular promoter construct that is often used in -vectored vaccines and is incorporated in the ChAdOx1 nCoV-19 vaccine. ALG may benefit from royalty income paid to the University of Oxford from sales of this vaccine by AstraZeneca and its sublicensees under the University's revenue sharing policy. ALG has given talks on COVID vaccines but has not benefited financially from these talks. MB reports advisory/speaker fees or grants to the institution from GSK, ViiV, Gilead, Janssen, Moderna, Pfizer, Valneva, MSD, Roche, Cipla, Mylan; and support for attending World AIDS conference registration for online attendance from ViiV. DRC reports a research grant to institution from Gilead Sciences; unpaid participation as IDMB member for FLARE trial (favipiravir in COVID-19); and unpaid role as British HIV Association Trustee Member. JG reports a research contract with institution from Novavax. CAC reports a research grant to institution from Moderna. PTH reports research grants to institution from Pfizer, Astra Zeneca, Moderna, Valneva, and Janssen; payment to institution for lectures, presentations, speakers bureaus, manuscript writing or educational events and for participation on a Data Safety Monitoring Board or Advisory Board from Novavax. PAK reports grants or contracts unrelated to this work from Vifor, Astellas, Evotec, Pharmacosmos, and Unicyte; consulting fees from Astra Zeneca, Vifor, Unicyte, and UCB; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Vifor, Astra Zeneca, Pfizer, Pharmacosmos, Napp, and Bayer; and support for attending meetings and/or travel from Pharmacosmos and Vifor. JP reports being co-applicant for the Haywood Foundation grant (Investigating the impact of the COVID-19 pandemic on people with arthritis 2021-23, £67,027) and for the NIHR/CRN COVID Innovation and Insight grant (Remotely

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TABLES

Table 1. Demographics and Baseline Characteristics for Participants in the Per-Protocol Efficacy Analysis Set

	NVX-CoV2373 (n = 6989)	Placebo (n = 7000)	Total (N = 13,989)
Age, years			
n	6989	7000	13,989
Mean (SD)	53.4 (14.81)	53.4 (14.83)	53.4 (14.82)
Median	56.0	56.0	56.0
Age group			
Under 65 years	5046 (72.2%)	5050 (72.1%)	10,096 (72.2%)
65 years and over	1943 (27.8%)	1950 (27.9%)	3893 (27.8%)
Sex			
Male	3594 (51.4%)	3616 (51.7%)	7210 (51.5%)
Female	3395 (48.6%)	3384 (48.3%)	6779 (48.5%)
Race*			
White	6637 (95.0%)	6650 (95.0%)	13,287 (95.0%)
Black or African American	26 (0.4%)	26 (0.4%)	52 (0.4%)
Asian	207 (3.0%)	217 (3.1%)	424 (3.0%)
Multiple	32 (0.5%)	28 (0.4%)	60 (0.4%)
Not reported	75 (1.1%)	69 (1.0%)	144 (1.0%)
Other	12 (0.2%)	10 (0.1%)	22 (0.2%)
Ethnicity[a]			
Hispanic or Latino	64 (0.9%)	51 (0.7%)	115 (0.8%)
Not Hispanic or Latino	6268 (89.7%)	6308 (90.1%)	12,576 (89.9%)
Not reported	537 (7.7%)	513 (7.3%)	1050 (7.5%)

Unknown	120 (1.7%)	127 (1.8%)	247 (1.8%)
Missing	0	1	1
Baseline BMI,[b] kg/m^2			
n	6836	6847	13,683
Mean (SD)	27.52 (5.321)	27.71 (5.637)	27.62 (5.482)
Median	26.70	26.80	26.70
Min, Max	14.2, 61.2	10.3, 87.4	10.3, 87.4
Baseline PCR			
Positive (+)	0	0	0
Negative (−)	6624 (94.8%)	6617 (94.5%)	13,241 (94.7%)
Missing	365	383	748
Day 21 PCR[c]‡			
Positive (+)	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Negative (−)	372 (5.3%)	360 (5.1%)	732 (5.2%)
Comorbidity status[d]			
Yes	3137 (44.9%)	3165 (45.2%)	6302 (45.0%)
No	3852 (55.1%)	3835 (54.8%)	7687 (55.0%)

Abbreviations: BMI, body-mass index; PCR, polymerase chain reaction.

Data are n (%) unless otherwise indicated. Percentages are based on per-protocol efficacy analysis set within each treatment and overall.

[a]Race or ethnic group was reported by the participants who could have listed more than one category.

[b]BMI is calculated as weight (kg) divided by squared height (m). A value of more than 30 kg/m^2 is considered to indicate obesity.

[c]Test performed only if the participant has any COVID-19 symptoms or significant exposure history between days 0 and 21.

[d]Comorbid participants are those identified who have at least one of the comorbid conditions reported as a medical history or have a screening BMI value greater than 30 kg/m^2. Coexisting conditions were recognized risk factors for severe COVID-19. These included chronic respiratory, cardiac, renal, neurologic, hepatic and certain immunocompromising conditions, as well as obesity.

Table 2. Overall Summary of Unsolicited Adverse Events (Safety Population)

Parameters	NVX-CoV2373 (n = 7569)		Placebo (n = 7569)	
	n (%)	N	n (%)	N
Any AEs	2075 (27.4%)	3134	1649 (21.8%)	2577
Any severe AEs	88 (1.2%)	114	87 (1.1%)	113
Any treatment-related AEs	880 (11.6%)	1145	369 (4.9%)	489
Any severe treatment-related AEs	15 (0.2%)	17	5 (< 0.1%)	5
Any MAAEs	355 (4.7%)	419	336 (4.4%)	402
Any treatment-related MAAEs	36 (0.5%)	46	17 (0.2%)	19
Any serious AEs	59 (0.8%)	75	61 (0.8%)	72
Any AEs leading to vaccination discontinuation	23 (0.3%)	29	28 (0.4%)	50
Any treatment-related AEs leading to vaccination discontinuation	7 (< 0.1%)	11	8 (0.1%)	9
Any AEs leading to study discontinuation	18 (0.2%)	18	13 (0.2%)	13
Any treatment-related AEs leading to study discontinuation	3 (< 0.1%)	3	1 (< 0.1%)	1

Any PIMMCs	6 (< 0.1%)	6	9 (0.1%)	9
Any AESIs: relevant to COVID-19	12 (0.2%)	18	35 (0.5%)	51

Abbreviations: AE, adverse event; AESI, adverse event of special interest; MAAE, medically attended adverse event; PIMMC, potential immune-mediated medical conditions.

All counts exclude reactogenicity AEs (selected preferred terms). Unsolicited AEs were classified as severe, medically attended, serious, leading to vaccination or study discontinuation, PIMMCs, or AESIs.

FIGURE LEGENDS

Figure 1. Participant Disposition and Status at the Time of Current Analysis

Participants were randomly assigned in a 1:1 ratio to receive NVX-CoV2373 or placebo. Participants were able to request to be unblinded or to withdraw from the study at any time. Those who were unblinded in the placebo arm may have received a currently authorized vaccine from the National Health Service, while those who were unblinded in the NVX-CoV2373 arm may have chosen to remain in the study for follow-up. Those who remained blinded in either of the two arms entered the blinded crossover or chose to remain blinded in the study and not enter the blinded crossover. For the current analysis participants were censored at the earliest of the date of unblinding (for any reason), date of receipt of an authorized vaccine Covid-19 vaccine, date of entering the blinded crossover (date of receiving a third study dose), date of early withdrawal, date of death or the data cut-off date of 27 July 2021.

Figure 2. Kaplan-Meier Plots of Efficacy of NVX-CoV2373 Against Symptomatic Covid-19 in the Per-Protocol and Intention-to-Treat Analysis Sets.

Shown is the cumulative incidence of symptomatic COVID-19 in the per-protocol population (Panel A), the intention-to-treat population (Panel B). The timing of surveillance for symptomatic COVID-19 began after the first dose (intention-to-treat population) and at least 7 days after the administration of the second dose (per-protocol population) of vaccine or placebo (ie, on Day 28) through a median of approximately 4.5 months of follow-up. yr, years.

Figure 3. Vaccine Efficacy of NVX-CoV2373 in Specific Subgroups

The efficacy of NVX-CoV2373 in preventing COVID-19 in various subgroups within the per-protocol population. Vaccine efficacy was defined as 1 minus the relative risk (NVX-CoV2373

vs placebo) and 95% confidence intervals were derived using Poisson regression with robust error variance (except where noted when the Clopper Pearson exact binomial method was utilized). Vaccine efficacy for the intention-to-treat population was assessed after dose 1. Data in non-White populations consisted of minority and multiple races, which were pooled to ensure that the subpopulations would be large enough for meaningful analyses. Comorbidity assessment is based on the Centers for Disease Control and Prevention definition of those at increased risk for COVID-19. The laboratory-confirmed symptomatic or asymptomatic and asymptomatic endpoints are defined in the text. Influenza vaccine co-administration was assessed as part of a pre-defined influenza vaccine co-administration substudy.

Figure 4. Emergence of the Alpha and Delta Variants during Study Assessment Periods in the United Kingdom

Surveillance data on SARS-CoV-2 strains that were present during the initial event-driven analysis and the current analysis periods. The Alpha variant emerged during the event-driven analysis and was present in over half the endpoints assessed at that time. In the subsequent time until the end of the placebo-controlled period the Alpha variant became the dominant variant and the United Kingdom saw the beginning of the emergence of the Delta variant.

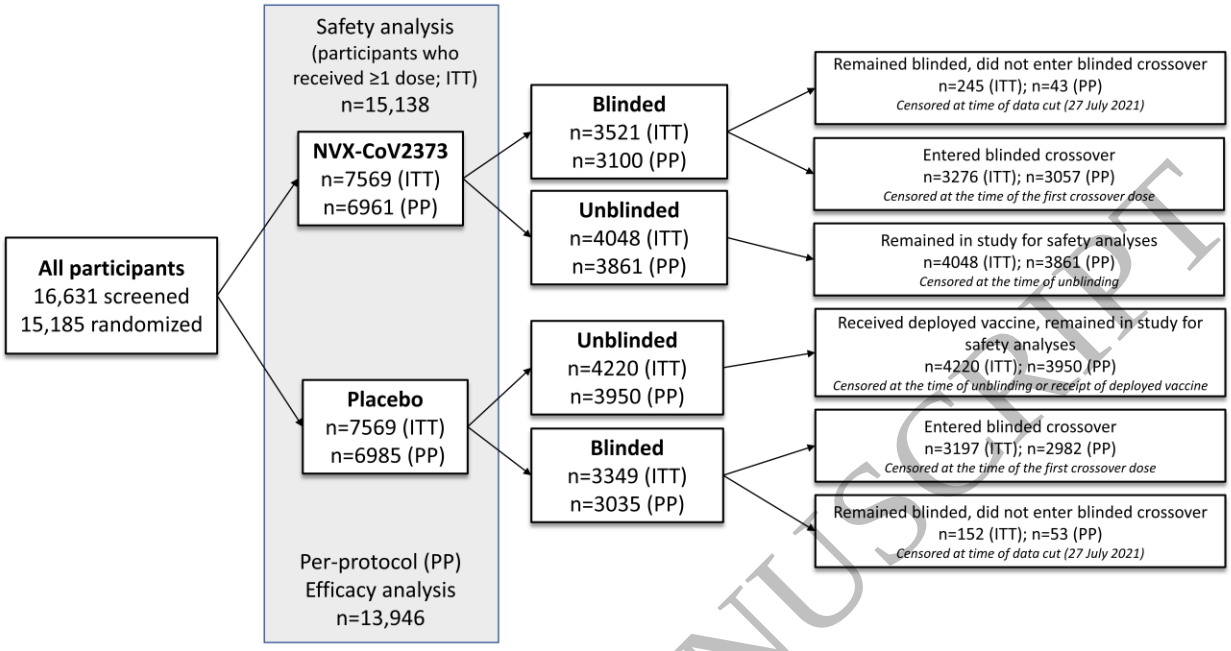
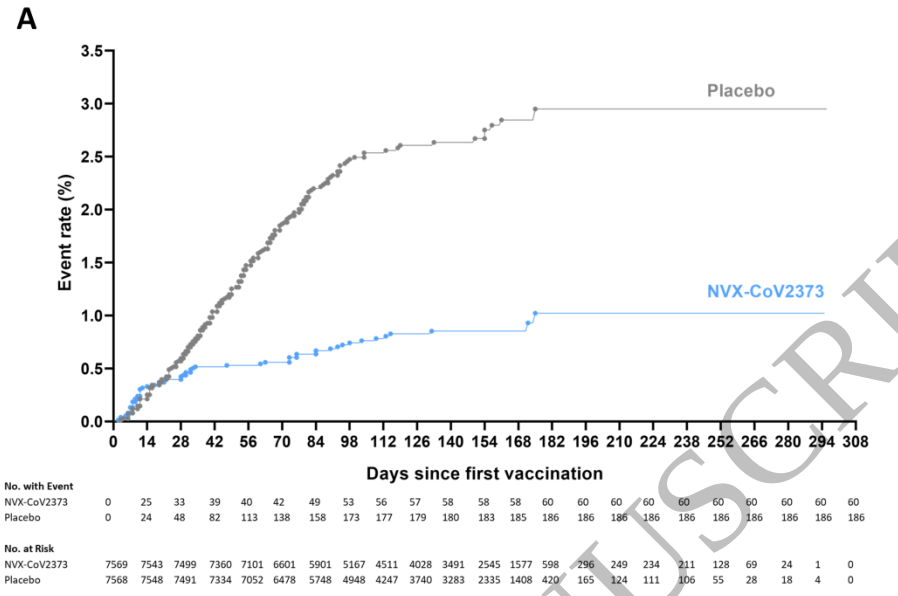


Figure 1
165x93 mm (x DPI)



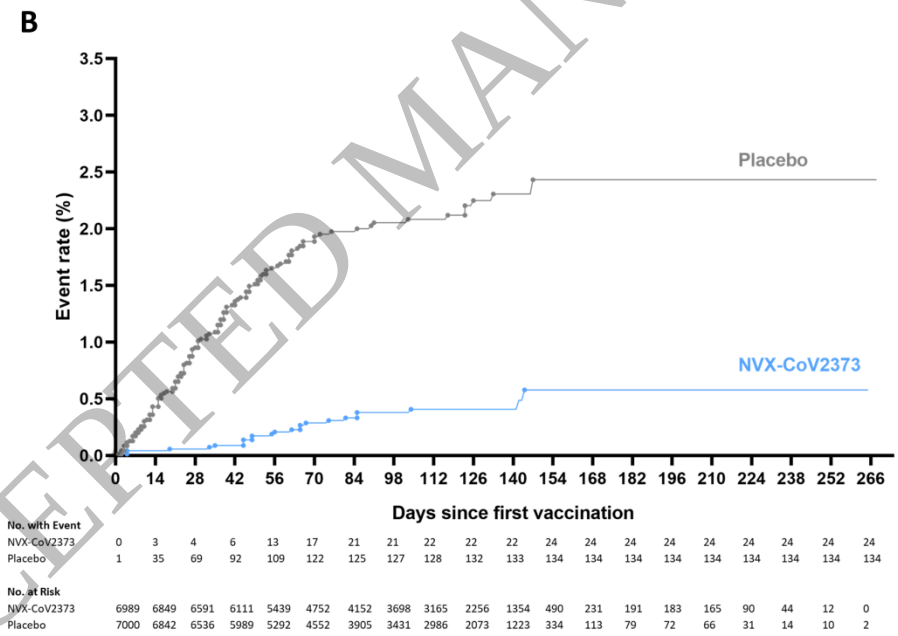


Figure 2
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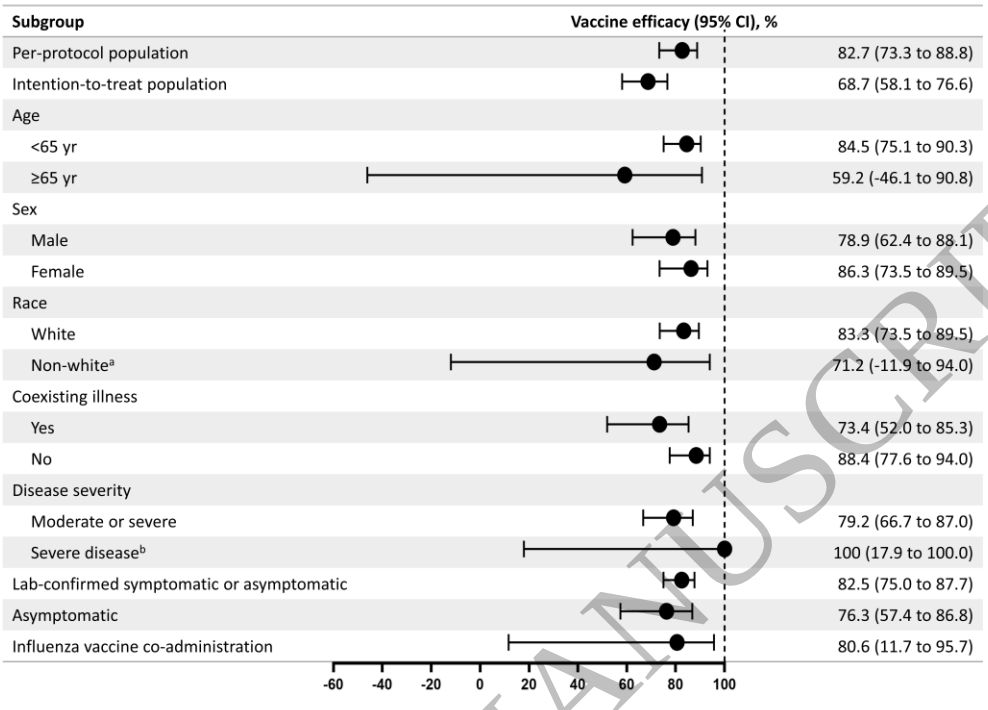
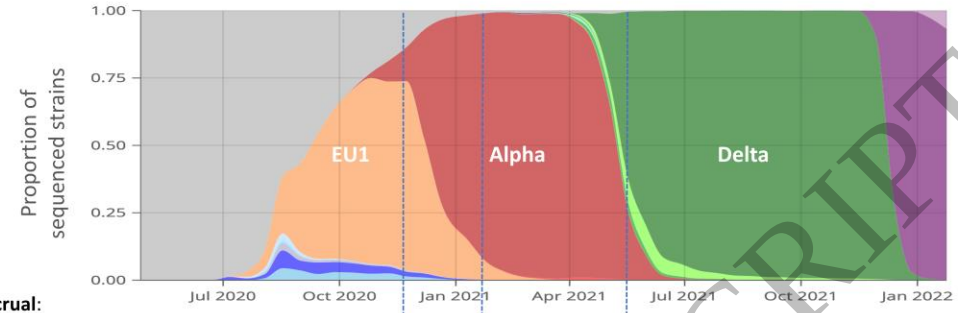


Figure 3
165x93 mm (x DPI)

Alpha (B.1.1.7) Variant Increased in Prevalence During Efficacy Collection Window



Efficacy Endpoint Accrual:
Event-driven analysis: 10 November 2020 – 24 January 2021
Current analysis: 10 November 2020 – 10 May 2021

Figure Source: Nextstrain.org

Figure 4
165x93 mm (x DPI)