Background document on the Novavax (NVX-CoV2373) vaccine against COVID-19

Background document to the WHO Interim recommendations for use of the Novavax (NVX-CoV2373) vaccine against COVID-19

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World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-novavax-nvx-cov2373-annexes

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Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on Novavax COVID-19 vaccines (NVX-CoV2373) to inform the discussions of SAGE at its meeting on 16 December 2021, which resulted in the issuance of the interim recommendations *(1)* and evidence to recommendation tables (annexes) *(2)*. These are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

This document refers to the COVID-19 vaccine developed by Novavax and the Serum Institute of India using the Novavax platform of recombinant protein nanoparticles formulated with Matrix M (NVX-CoV2373), and authorized under the emergency use listing (EUL) procedure by WHO. It is based on the Novavax core non-clinical and clinical data for regulatory evaluation. NVX-CoV2373 will be marketed as Nuvaxovid (Novavax) and COVOVAX (Serum Institute of India). These vaccines are considered fully equivalent, although they are produced at different manufacturing sites and assigned different product names. In the subsequent text, the vaccine will be referred to as NVX-CoV2373.

Context

NVX-CoV2373 is a recombinant spike protein nanoparticle-based vaccine. It contains the full-length SARS-CoV-2 spike protein and a saponin-based Matrix-M adjuvant. Protein-based vaccines cannot replicate and therefore cannot infect individuals.

Matrix-M is an adjuvant added to enhance the immune response to the vaccine. In studies of Matrix-M, the adjuvant was found to be antigen dose-sparing, and induced cluster of differentiation (CD)4+ T-cell responses that were biased towards a T helper 1 (Th1) response *(3)*. Matrix-M is a novel saponin-based adjuvant that has been administered in studies of NVX-CoV2373 (~30 000 recipients across phase 1 to phase 3 trials) and in prelicensure studies targeting other pathogens (~4200 recipients overall), but has not previously been used in any licensed vaccine. The adjuvant has been used in a total of 29 clinical trials (14 sponsored by Novavax and 15 sponsored by other collaborating entities) in the United States of America, United Kingdom, mainland Europe, Australia, and Africa. Of these, 19 have been completed (9 sponsored by Novavax) and 10 are ongoing, and may or may not have unblinded data available. The integrated safety analysis of Novavax-sponsored studies showed that, in all age groups, the rate of solicited adverse events (AEs) was higher in the Matrix-M adjuvanted groups than in the unadjuvanted vaccine or placebo groups after both the first and second vaccinations. These differences were largely due to injection site pain.

Characteristics of NVX-CoV2373 (COVID-19) vaccine

Composition

NVX-CoV2373 includes the following ingredients: SARS-CoV-2[1] recombinant spike protein (5 µg per dose) with Matrix-M adjuvant (50 µg per dose), constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein based on the GenBank gene sequence MN908947 (Wuhan-Hu-1 isolate) nucleotides 21563–25384; inactive ingredients include disodium hydrogen phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride and Polysorbate 80. The adjuvant Matrix-M contains 42.5 µg of fraction-A and 7.5 µg of fraction-C of *Quillaja saponaria* Molina extract per 0.5 ml dose.

Dosing regimen

NVX-CoV2373 is administered intramuscularly in 2 doses (0.5 ml per dose) given 3-4 weeks apart. It is standard practice for individuals who receive a first dose of NVX-CoV2373 to complete the vaccination course with NVX-CoV2373.

[1] SARS-CoV-2 recombinant spike protein is produced by DNA technology using a baculovirus expression system in an insect cell line derived from Sf9 cells of the *Spodoptera frugiperda.*

Stability and shelf-life

A shelf-life of 9 months is proposed. The vaccine is provided as a refrigerated suspension stored at 2–8 °C in a single-dose vial or a vial containing 10 doses (0.5 ml each). The vials should be protected from light. After the first dose has been withdrawn, the vial may be held at 2–8 °C for up to 6 hours. The vial should be discarded if the vaccine is not used within these times.

The expiry date of the vaccine is indicated on the label and packaging.

Drug product description

NVX-CoV2373 is a sterile suspension for intramuscular injection.

Container

The vaccine is provided in single-dose (0.5 ml) and multidose glass vials (10 doses).

Developmental and reproductive toxicity

Developmental and reproductive toxicity (DART) studies compliant with good laboratory practice (GLP) were performed in Sprague Dawley rats, with dosing prior to conception and during gestation. These studies investigated reproductive performance, embryonic and fetal development *in utero,* and effects in neonates from birth until weaning. There were no adverse findings for fertility, pregnancy, lactation, or development of the embryo, fetus and offspring through postnatal day 21.

Pharmacology

A comprehensive pharmacology programme evaluating the NVX-CoV2373 vaccine was undertaken, comprising multiple studies to evaluate both humoral and cell-mediated immune responses in rodents and nonhuman primates. Robust humoral immune responses, including anti-spike (anti-S) immunoglobin G (IgG), hACE2 binding inhibiting, and wild-type virus-neutralizing antibodies, were generated following vaccination, with the response dominated by the T helper 1 (Th1) phenotype.

Administration of NVX-CoV2373 to mice produced a Th1-dominant response, as demonstrated by induction of strong Th1-type CD4+ T-cell responses. These included multifunctional effector phenotypes (producing interferon gamma (IFNγ), tumour necrosis factor alpha (TNFα), and interleukin 2 (IL2)), which were generally induced at much higher levels than interleukin 4 (IL4)-producing Th2 cells. NVX-CoV2373 vaccine administered to baboons at human dose levels also induced strong Th1-dominant CD4+ T-cell responses, which included polyfunctional effector phenotypes. In rhesus macaques, immunization with NVX-CoV2373 elicited high levels of both S-specific and receptor-binding domain (RBD)-specific antibodies. Changes in circulating immune cell abundance postvaccination were consistent with typical responses to a potent adjuvant, as well as recruitment of lymphocytes to lymphoid organs. B-cell responses after the second dose were consistent with a rapid recall of memory B cells. T-cell responses again indicated a Th1-skewed response, and the presence of circulating T follicular helper (Tfh) cells after the boost suggested an ongoing germinal centre reaction.

Protective efficacy studies evaluating live virus challenge following vaccination, with necropsy and histopathological evaluations, have also been conducted across multiple species, including mice, hamsters, cynomolgus macaques, and rhesus macaques *(4)*. The vaccine was immunogenic in all species, inducing high titres of anti-S IgG antibodies, as well as functional hACE2 receptor-binding-inhibiting and virus-neutralizing antibodies. NVX-CoV2373 also elicits multifunctional CD4+ and CD8+ T cells, CD4+ follicular helper T cells (Tfh), and antigen-specific germinal center (GC) B cells in the spleen.

Animals vaccinated with NVX-CoV2373 were protected from viral replication in the upper and lower respiratory tract following challenge with live SARS-CoV-2. Importantly, there was no evidence of vaccine-enhanced disease following exposure to SARS-CoV-2 virus in any study *(5)*.

Single-dose toxicity

No single-dose toxicity studies have been conducted.

Repeat-dose toxicity

Toxicity testing of NVX-CoV2373 includes a completed GLP repeat-dose toxicology study conducted in New Zealand White (NZW) rabbits. Effects were consistent with immune stimulation, i.e. transiently increased C-reactive protein (CRP), globulin and fibrinogen, and reversible injection site inflammation. Microscopic findings at the injection sites consisted of minimal to moderate subacute inflammation characterized by mixed inflammatory infiltrates of heterophils, macrophages and lymphocytes. Inflammation was generally similar between vaccine groups with and without Matrix-M1 and similar in incidence and severity across all studies.

Clinical studies

The pivotal safety, efficacy, and immunogenicity data informing registration of the vaccine are derived from the following studies.

- **2019nCoV-101 (part 1).** A 2-part, phase 1/2, randomized, observer-blinded study to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects *(6)*.
    - This is part 1 (phase 1 first-in-human) of 2019nCoV-101. It included participants aged 18–59 years, and evaluated the vaccine with and without adjuvant, as a bedside-mixed antigen and adjuvant.
- **2019nCoV-101 (part 2).** A 2-part, phase 1/2, randomized, observer-blinded study to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.
    - This is part 2 (phase 2) of 2019nCoV-101. It included participants aged 18–84 years, and evaluated the vaccine with adjuvant as a co-formulated drug product (as in the remaining phase 2 and phase 3 studies) *(7)*.
- **2019nCoV-501.** A phase 2a/b, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.
- **2019nCoV-302.** A phase 3, randomized, observer-blinded, placebo-controlled trial to evaluate the efficacy and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants 18–84 years of age in the United Kingdom *(8)*.
- **2019nCoV-301.** A phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants ≥18 years with a paediatric expansion in adolescents (12 to <18 years) *(9)*.

Studies in other populations (e.g. children with and without comorbidities) are also planned.

Immunogenicity studies in humans

Clinical study 2019nCoV-101 (part 1) compared two-dose regimens of 5 µg or 25 µg NVX-CoV2373 with 50 µg Matrix-M adjuvant administered 21 days (+ 7 days) apart, a one-dose 25 µg adjuvanted regimen, a two-dose 25 µg unadjuvanted regimen, and placebo in healthy adults aged 18–59 years. Both adjuvanted 2-dose regimens induced robust immune responses (anti-S protein IgG, wild-type neutralizing antibodies, and hACE2 receptor-binding inhibition), which peaked 2 weeks after the second vaccination (day 35). Matrix-M adjuvant was antigen-sparing and induced high levels of functional antibodies and a Th1-biased immune response. No dose response was seen between the 5-µg and 25-µg doses. A strong correlation was observed between anti-S protein IgG levels or hACE2 receptor-binding inhibition and neutralizing antibodies from day 35 through day 189 *(6)*.

Two-dose regimens of 5 µg or 25 µg NVX-CoV2373 with 50 µg Matrix-M adjuvant, administered 21 days (+ 7 days) apart as a co-formulated product in part 2 of clinical study 2019nCoV-101, showed similar results to part 1 at day 35, in healthy adults aged 18–84 years, regardless of baseline SARS-CoV-2 serostatus. There was an approximate 2-fold attenuation of immune response in participants aged 60–84 years. Collectively, the data from part 1 and part 2 supported selection and further development of the two-dose 5 µg adjuvanted vaccine regimen *(7)*.

A two-dose regimen of NVX-CoV2373, administered 21 days (+ 7 days) apart, similarly induced robust immune responses (anti-S protein IgG and neutralizing antibody) relative to placebo in adults aged 18–84 years in clinical studies 2019nCoV-302 (7) and 2019nCoV-301 *(9)* with higher levels in the younger adult cohort (18–64 years) than in those aged 65–84 years, but with similarly high seroconversion rates (see Table 1).

Table 1. Neutralizing antibody titres by day and age group for the two-dose schedule

Days since first dose	Metric	18–64 years (*n*=554)		≥65 years (*n*=207)	
		Vaccination (*n*=270)	Placebo (*n*=284)	Vaccination (*n*=111)	Placebo (*n*=96)
A. United Kingdom (study 302)[a, b]					
Day 0 (baseline)	GMT	10	10	10	10
	95% CI	10–10	10–10	10–11	10–10
	Median	10	10	10	10
	Min, Max	10, 20	10, 40	10, 160	10, 10
Day 35 (14 days post-dose 2)	GMT	1241	11	908	10
	95% CI	1069–1441	10–11	720–1145	10–10
	Median	1280	10	1280	10
	Min, Max	10, 20 480	10, 5120	10, 10 240	10, 10
B. Mexico and USA (study 301) [b, c]					
Day 0 (baseline)	GMT	11	10	10	10
	95% CI	10–11	10–10	10.0–11	10–10
	Median	10	10	10	10
	Min, Max	10, 10 240	10, 10	10, 2560	10, 20
Day 35 (14 days post-dose 2)	GMT	1293	11	902	11
	95% CI	1128–1482	10–11	764–1063	10–12
	Median	1280	10	1280	10
	Min, Max	10, 40 960	10, 640	10, 20 480	10, 640

[a] Immunogenicity data are based on the neutralization assay subset of the per-protocol immunology analysis set. Data lock date 15 March 2021.

[b] Neutralizing antibodies specific for SARS-CoV-2 wild-type virus were measured using a validated virus neutralizing assay (VNA) with wild-type virus (SARS-CoV-2 hCoV-19/Australia/VIC01/2020 [GenBank MT007544.1]; 360biolabs, Melbourne, Australia). The lower limit of quantification (LLOQ) for this assay was a titre of 20, with titres below this level documented as 10.

[c] Data lock date 9 August 2021.

Immunogenicity for variants of concern

During a phase 2 study in Australia and the USA, in blood samples collected 14 days after the second dose of NVX-CoV2373, antibody responses were 4-fold, 4.8-fold, and 3-fold lower for alpha, beta, and delta variants, respectively, than for the ancesteral virus.

Efficacy studies

The following discussion relates to the phase 2a/b trial in South Africa (study 501) and two phase 3 trials (studies 301 and 302) in Mexico/USA and the United Kingdom.

Case definitions

Case definitions for mild, moderate, and severe COVID-19 are given in Box 1. Study endpoints are described in Box 2 *(9)*.

Box 1. Case definitions for mild, moderate and severe COVID-19 in the phase 2a/b and phase 3 studies

The case definition for symptomatic COVID-19 was a SARS-CoV-2-positive nasopharyngeal swab, determined by real-time polymerase chain reaction (RT-PCR), plus symptoms as described below.

The disease was considered mild if, at any time during the course of observation, there was one or more of the following:

- fever (defined subjectively or objectively, regardless of use of antipyretic medications);
- new onset cough;
- two or more additional COVID-19 symptoms:
    - new onset or worsening of shortness of breath or difficulty breathing compared with baseline;
    - new onset fatigue;
    - new onset generalized muscle or body aches;
    - new onset headache;
    - new loss of taste or smell;
    - acute onset of sore throat, congestion, or runny nose;
    - new onset nausea, vomiting, or diarrhoea.

The case was considered moderate if there was one or more of the following:

- high fever (≥38.4 °C) for ≥3 days (not necessarily contiguous, and regardless of use of antipyretic medications);
- evidence of significant lower respiratory tract infection (LRTI):
    - shortness of breath (or breathlessness or difficulty breathing), with or without exertion (greater than baseline);
    - tachypnoea: 24–29 (20-29 for the 302 and 501 studies) breaths per minute at rest;
    - oxygen saturation (SpO_2): 94– 95% on room air;
    - abnormal chest X-ray or computerized tomography (CT) scan consistent with pneumonia or LRTI;
- adventitious sounds on lung auscultation (e.g. crackles/rales, wheeze, rhonchi, pleural rub, stridor).

The case was considered severe if there was one or more of the following:

- tachypnoea: ≥30 breaths per minute at rest;
- resting heart rate ≥125 beats per minute;
- SpO2: ≤93% on room air or PaO_2/FiO_2 <300 mmHg;
- high-flow O_2 therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (e.g. continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]);
- mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
- dysfunction or failure of one or more major organ systems, defined by diagnostic testing, clinical syndrome or intervention, and including any of the following:
    - acute respiratory failure, including acute respiratory distress syndrome (ARDS);
    - acute renal failure;
    - acute hepatic failure;
    - acute right or left heart failure;
    - septic or cardiogenic shock (defined as systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg);
    - acute stroke (ischaemic or haemorrhagic);
    - acute thrombotic event (myocardial infarction, deep vein thrombosis, pulmonary embolism);
    - requirement for: vasopressors, systemic corticosteroids, or haemodialysis;
- admission to an intensive care unit (ICU);
- death.

Box 2a. Primary and secondary efficacy and immunogenicity endpoints in the phase 2a/b and phase 3 studies : Study 2019nCoV-301

Primary efficacy endpoint

- First episode of RT-PCR-positive mild, moderate, or severe COVID-19.

Key efficacy secondary endpoint

- First episode of RT-PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification.

Secondary efficacy endpoints

- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
- ANY symptomatic SARS-CoV-2 infection, defined as: RT-PCR-positive nasal swab and ≥ 1 of any of the following symptoms:
    - Fever.
    - New onset cough.
    - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
    - New onset fatigue.
    - New onset generalized muscle or body aches.
    - New onset headache.
    - New loss of taste or smell.
    - Acute onset of sore throat, congestion or runny nose.
    - New onset nausea, vomiting or diarrhea.
- Description of course, treatment and severity of COVID-19 reported after an RT-PCR-confirmed case via the Endpoint Form.

Secondary immunogenicity endpoints

- Neutralizing antibody titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.[a]
- Serum immunoglobulin G (IgG) levels to SARS-CoV-2 S protein, human angiotensin converting enzyme 2 (hACE2) inhibition titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.[a]
- Serum IgG levels to SARS-CoV-2 spike protein, microneutralization (MN) and hACE2 inhibition titers from Immunogenicity Population at Months 12, 18 and 24.[a]
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, immediately prior to administration of the crossover set of vaccinations, and at Months 12, 18 and 24 will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.[a]
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.[a]
- IgG antibodies to SARS-CoV-2 rS at approximately 35 days after the first crossover vaccination in approximately 300 active vaccine recipients 18 to ≤ 64 years of age enrolled at selected study sites.[a]
- Neutralizing antibody response at Day 35 for all adolescent participants seronegative to antiSARSCoV2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.[a]

[a] Objectives and endpoints not addressed in the interim report because of incompleteness or unavailability of data are noted in the table; this includes immunogenicity data and data from the period after blinded crossover.

Box 2b. Primary and secondary efficacy and immunogenicity endpoints in the phase 2a/b and phase 3 studies : Study 2019nCoV-302

Study 2019nCoV-302

Primary efficacy endpoint

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.

Key efficacy secondary endpoint

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic moderate or severe COVID-19 with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.

Secondary efficacy endpoints

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic severe COVID-19 with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.
- First occurrence of COVID-19 requiring hospitalization, intensive care unit (ICU) admission, or mechanical ventilation linked to any virologically confirmed (by PCR to SARS-CoV-2) COVID-19 with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild COVID-19 (with no progression to moderate or severe COVID-19 during the course of the COVID-19 episode) with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in adult participants, regardless of their serostatus at baseline.[a]
- First occurrence of laboratory-confirmed (by PCR or N-protein serology to SARS-CoV-2) symptomatic or asymptomatic COVID-19 with onset from at least 7 days after second study vaccination (eg, Day 28) in the initial set of vaccinations in adult participants with negative serostatus at baseline.[a]
- Relative vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs crossover (delayed) active vaccine recipients.[a]

Secondary immunogenicity endpoints

- Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA at Day 0 (baseline) and Day 35 (14 days after second study vaccination.
- Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA at Crossover Day 0 visit (baseline) and Crossover Day 35 visit (14 days after second study vaccination).[a]

[a] Endpoints not addressed in the interim report because of incompleteness or unavailability of data are noted in the tables 3 and 4 below; this includes immunogenicity data and data from the period after blinded crossover.

Box 2c. Primary and secondary efficacy and immunogenicity endpoints in the phase 2a/b and phase 3 studies : Study 2019nCoV-501

Study 2019nCoV-501

Primary efficacy endpoint

- Positive (+) PCR-confirmed SARS-CoV-2 illness with symptomatic mild, moderate, or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy human immunodeficiency virus (HIV)-negative and medically stable HIV-positive adult participants, analyzed overall, with a lower bound CI of > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points during the initial vaccination period.

Key efficacy secondary endpoint

- Positive (+) PCR-confirmed SARS-CoV-2 illness with symptomatic mild, moderate, or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants, analyzed separately, with a lower bound CI of > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points during the initial vaccination period and in a subset of participants in the crossover period.
- (+) PCR-confirmed SARS-CoV-2 illness with symptomatic mild or moderate; OR symptomatic moderate or severe COVID-19 in serologically naïve (to SARS-CoV-2), healthy HIV-negative and medically stable HIV-positive adult participants, with a lower bound CI > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points.

Secondary efficacy endpoints

- Positive (+) PCR-confirmed SARS-CoV-2 illness with asymptomatic, symptomatic virologically confirmed, mild, moderate, or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants from 7 days after the second vaccine dose (eg, Day 28).
- (+) PCR-confirmed SARS-CoV-2 with COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants, in terms of individual strata of symptomatic virologically confirmed, mild, moderate, or severe categories of COVID-19 as previously described.
- Incidence, maximum severity score, and symptom duration of SARS-CoV-2 infection by classification of symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants, overall and by age strata. Should COVID-19 illness scoring be substantially validated at the time of study start, application of the standard scoring may be applied.

Secondary immunogenicity endpoints

- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by enzyme-linked immunosorbent assay (ELISA) using geometric mean titre (GMT) OR seroconversion rate (SCR) at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in healthy HIV-negative and medically stable HIV-positive adult participants, for all participants in the initial vaccination period and for a subset of participants in the crossover vaccination period, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). Derived/calculated endpoints based on these data will include geometric mean ELISA units (GMEUs), geometric mean fold rise (GMFR), and SCR. SCR is defined as the percentage of participants with a post-vaccination titer ≥ 4-fold over naïve background and ≥ 2-fold over preexisting titer. Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.
- Epitope-specific immune responses to the SARS-CoV-2 rS protein receptor binding domain measured by serum titers in a human angiotensin-converting enzyme 2 (ACE2) receptor binding inhibition assay, described across study time points, to include GMT, GMFR, SCR, and seroresponse rate (SRR) in healthy HIV-negative and medically stable HIV-positive adult participants, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). SRR is defined as the proportion of participants with rises in titers exceeding the 95th percentile of placebo participants at the same time point and based on prior SARS-CoV-2 exposure.
- Neutralizing antibody activity at Day 35 and across later study time points relative to baseline in healthy HIV-negative and medically stable HIV-positive adult participants in the initial vaccination period by absolute titers and change from baseline, including SCR (≥ 4fold change) and SRR, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2) to investigate whether baseline status (+/-) impacts response.
- Neutralizing antibody activity relative to baseline in healthy HIV negative and medically stable HIV-positive adult participants in the initial vaccination period and in a subset of participants in the crossover vaccination period, combined, by absolute titers and change from baseline, including SCR (≥ 4fold change) and SRR, regardless of baseline serostatus and stratified by baseline serostatus (to SARSCoV-2) to investigate whether baseline status (+/-) impacts response.

Participant characteristics

Table 2 provides the demographic characteristics of the study participants.

Table 2. Demographic characteristics of participants in the per-protocol efficacy populations of the phase 2a/b and phase 3 studies

Parameter	**NVX-CoV2373** *n* (%)	**Placebo** *n* (%)
Study 2019nCoV-301 (Mexico and USA)		
Number of participants	17 312	8140
Age, years (mean ± SD)	46.3 (14.9)	46.6 (14.8)
Range (years)	18–95	18–90
18 to ≤ 64 years	15 264 (88.2)	7194 (88.4)
≥ 65 years	2048 (11.8)	946 (11.6)
Females	8262 (47.7)	4009 (49.3)
Males	9050 (52.3)	4131 (50.7)
At high risk from COVID-19	16 493 (95.3)	7737 (95.0)
Pre-existing medical conditions		
Any comorbidity	8117 (46.9)	3910 (48.0)
Cardiovascular disease	191 (1.1)	91 (1.1)
Chronic lung disease	2442 (14.1)	1218 (15.0)
Diabetes mellitus type 2	1303 (7.5)	677 (8.3)
Stable kidney disease	109 (0.6)	50 (0.6)
Obesity (BMI ≥30 kg/m^2)	6400 (37.0)	3070 (37.7)
HIV infection	128 (0.7)	38 (0.5)
Study 2019nCoV-302 (United Kingdom)		
Number of participants	7020	7019
Age, years (mean ± SD)	53.4 (14.8)	53.4 (14.8)
Range (years)	18–84	18–84
18 to ≤ 64 years	5067 (72.2)	5062 (72.1)
≥ 65 years	1953 (27.8)	1957 (27.9)
Females	3411 (48.6)	3390 (48.3)
Males	3609 (51.4)	3629 (51.7)
Pre-existing medical conditions		
Any comorbidity	2663 (37.9)	2730 (38.9)
Cardiovascular disease	86 (1.2)	109 (1.6)
Chronic lung disease	754 (10.7)	790 (11.3)
Diabetes mellitus type 2	327 (4.7)	310 (4.4)
Stable kidney disease	20 (0.3)	23 (0.3)
Obesity (BMI ≥30 kg/m^2)	1784 (25.4)	1863 (26.5)
HIV infection	8 (0.1)	11 (0.2)

Parameter	NVX-CoV2373 *n* (%)	Placebo *n* (%)
Study 2019nCoV-501 (South Africa)		
Number of participants	1408	1362
Age, years (mean ± SD)	32.3 (13.2)	32.8 (13.6)
Range (years)	18-84	18-83
18 to ≤ 64 years	1346 (95.6)	1297 (95.2)
≥ 65 years	62 (4.4)	65 (4.8)
Females	557 (39.6)	503 (36.9)
Males	851 (60.4)	859 (63.1)
Body Mass Index Mean (± SD)	24.7 (5.7)	24.5 (5.5)
Pre-existing Conditions		
HIV positive	77	73

Summary of results

Across the phase 2a/b and two pivotal phase 3 vaccine efficacy (VE) studies, a two-dose regimen of NVX-CoV2373, administered 21 days (+ 7 days) apart, met the prespecified criteria of their respective studies for success in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19, with onset from at least 7 days after the second vaccination in adults ≥18 years of age who were serologically negative to SARS-CoV-2. The two phase 3 trials independently demonstrated ~90% efficacy against COVID-19 with a lower bound confidence interval (LBCI) >30%, as well as 100% efficacy against severe disease (see Table 3).

In study 2019nCoV-501 in South Africa, the VE in achieving the primary efficacy endpoint was 49% (95% CI: 6–73) with an LBCI >0% (official event-driven analysis) and 49% (95% CI: 28–63) with an LBCI >0% (complete analysis) for the combined population of HIV-negative and HIV-positive participants. This was during a period in which the beta variant was predominant in the country. The VE in achieving the key secondary efficacy endpoint in HIV-negative participants was 55% (95% CI: 36–69).

In study 2019nCoV-302 in the United Kingdom, the VE in achieving the primary efficacy endpoint was 90% (95% CI: 75–95) with an alpha-adjusted LBCI > 30% (interim analysis) and 90% (95% CI: 80–95) with an LBCI > 30% (final analysis). This was during a period in which the B.1.1.7 (alpha) variant was predominant in the country. Additional secondary efficacy endpoints were also achieved, including a VE against moderate or severe COVID-19 of 87% (95% CI: 74–94) and a VE of 89% (95% CI: 20–100) in adults over the age of 65 years.

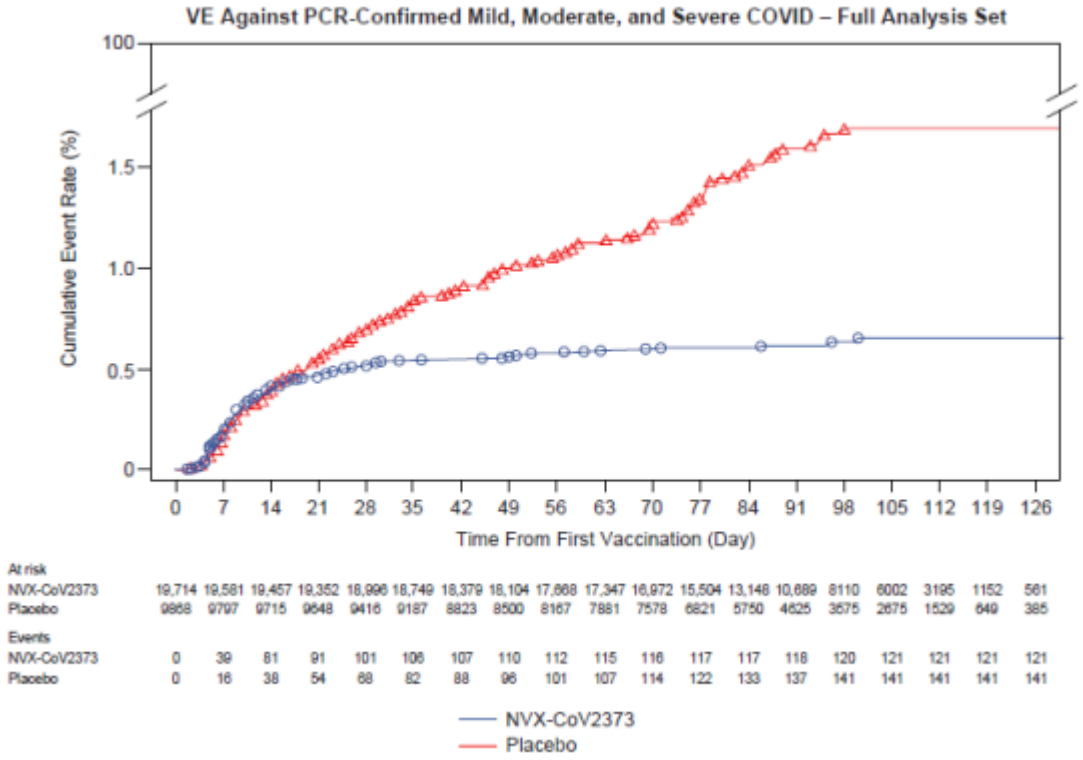
In study 2019nCoV-301 in Mexico and the USA, the VE in achieving the primary efficacy endpoint was 90% (95% CI: 83–95) with an LBCI >30%. This was during a period in which variants non-identical with the Wuhan-Hu-1 prototype strain and considered variants of concern and variants of interest were predominant in the countries. Additional secondary efficacy endpoints showed VEs of 100% (95% CI: 81–100) for SARS-CoV-2 variants not considered VOCs or VOIs and 93.18% (95% CI: 84–97) for SARS-CoV-2 variants considered VOCs or VOIs and a VE of 57% (95% CI:-487–97) for any symptomatic COVID-19 in those over 65 years of age.

Kaplan Meier plots for the two phase 3 clinical trials are presented in Figure 1.

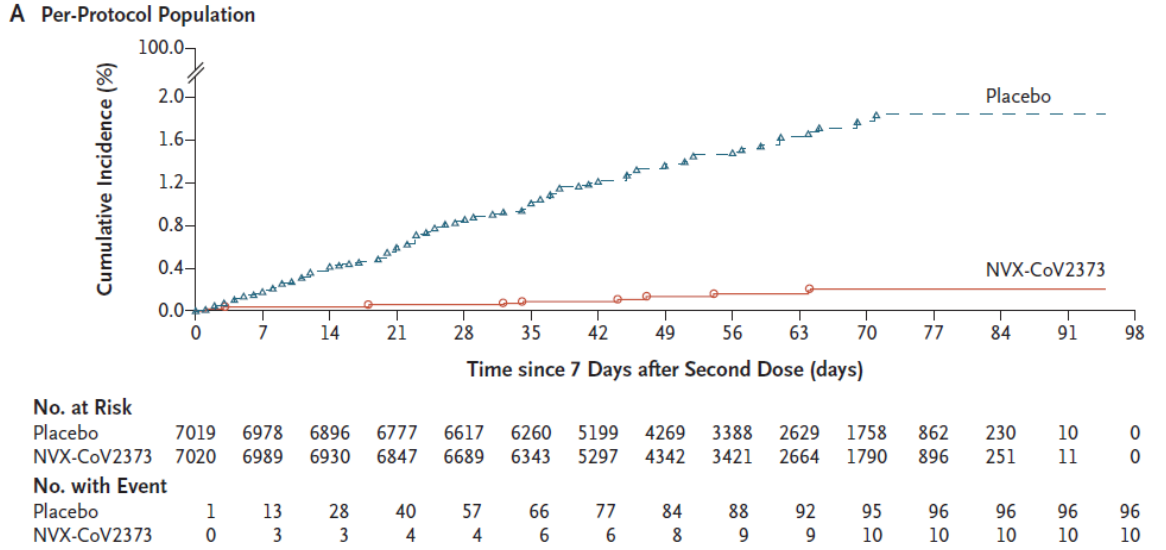
Participants in Studies 2019nCoV-302 and 2019nCoV-501 will continue to be followed for 1 year and participants in Study 2019nCoV-301 for 2 years for assessment of both safety and efficacy against COVID-19. Given the nature of the pandemic at the study locations, a blinded crossover design was implemented after achieving 2 months of placebo-controlled safety follow-up so that all participants could receive an active COVID-19 vaccine as soon as possible.

Figure 11. Kaplan Meier plot of full analysis of phase 3 studies from the first dose of NVX-CoV2373 or placebo; per-protocol symptomatic COVID-19 cases were from at least 7 days after the second dose (i.e. day 28) through approximately 3 months of follow-up after the first vaccination up to initiation of the blinded crossover or unblinding or receipt of vaccine.

A. Mexico and USA.



B. United Kingdom



Efficacy against severe COVID-19

Across the three studies, which included an overall sample size of 42 261 in the primary VE endpoint calculations (25 740 NVC-CoV2373 recipients and 16 521 placebo recipients), there were 14 cases of severe COVID-19 occurring at least 7 days after the second vaccine dose, all of which occurred in the placebo group.

Efficacy in persons with previous SARS-CoV-2 infection (based on seropositivity at baseline)

One case of COVID-19 occurring in the vaccine group (combined) and two cases occurring in the placebo group were seropositive for SARS CoV-2 IgG at baseline.

Efficacy against new variants of concern

In the phase 2 study in South Africa, which was completed during a period in which the beta variant was predominant, the VE in relation to the primary efficacy endpoint was 49.4% (95% CI: 6.1–72.8) in the official event-driven analysis and 49% (95% CI: 28–63) in the complete analysis, both of which included HIV-negative and HIV-positive participants.

In the phase 3 study 2019nCoV-302 (United Kingdom), 8 cases of COVID-19 due to the alpha variant occurred in the vaccine group and 58 cases in the placebo group, giving a VE against the alpha variant of 86.3% (95% CI: 71.3–93.5)*(8)*). In study 2019nCoV-301 (Mexico and USA), 4 cases of COVID-19 due to the alpha variant occurred in the vaccine group and 27 cases in the placebo group, giving a VE against the alpha variant of 94% (95% CI: 82–98) *(9)*).

Table 3 summarizes the vaccine efficacy results from the two phase 3 clinical trials.

Table 3. Vaccine efficacy results from the phase 2a/b and phase 3 clinical studies[a]

	Vaccine group		Placebo group		VE% (95% CI)	Notes
Group	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**		
All (vaccine efficacy against confirmed mild, moderate, or severe COVID-19 disease[b])						
2019nCoV-302	7020	10	7019	96	90 (80–95)	
2019nCoV-301	17 312	14	8140	63	90 (83–95)	
2019nCoV-501	1408	51	1362	96	49 (28 -63)	
Sex						
2019nCoV-302						
Males	3609	5	3629	43	88 (70–95)	
Females	3411	5	3390	53	91 (77–96)	
2019nCoV-301						
Males	9050	5	4131	23	91 (76–96)	
Females	8262	9	4009	40	90 (79–95)	
2019nCoV -501						
Males	1252	NA[d]	1266	NA[d]	NA	
Female	947	NA[d]	922	NA[d]	NA	
Age group (years)						
2019nCoV-302 (symptomatic mild, moderate, or severe COVID-19 disease only)						
All ages	7020	10	7019	96	90 (80–95)	Analysis not available for any symptomatic[c] COVID-19 disease.
18–64	5067	9	5062	87	90 (80–95)	
≥65	1953	1	1957	9	89 (20–100)	
2019nCoV-301 (symptomatic mild, moderate, or severe COVID-19 disease only)						
All ages	17 312	14	8140	63	90 (83–95)	
18–64	15 264	12	7194	61	91 (84–95)	
≥65	2048	2	946	2	57 (-487–97)	

	Vaccine group		Placebo group		VE% (95% CI)	Notes
Group	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**		
2019nCoV-301 (any symptomatic COVID-19 disease[c])						
All ages	17 312	14	8140	64	91 (83–95)	
18–64	15 264	12	7194	62	92 (84–95)	
≥65	2048	2	946	2	57 (-487–97)	
2019nCoV -501 (symptomatic mild, moderate, or severe COVID-19 disease only)						
All ages	1408	51	1362	96	49 (28 - 63)	
Region (confirmed symptomatic COVID-19 disease)						
United Kingdom (2019nCoV-302)	7020	10	7019	96	90 (80–95)	
USA (2019nCoV-301)	16 294	14	7638	62	90 (83–95)	
Mexico (2019nCoV-301)	1018	0	502	1	100 (-1792–100)	
South Africa (2019nCoV-501)	1408	51	1362	96	49 (28 - 63)	
Comorbidity (confirmed symptomatic COVID-19 disease)						
2019nCoV-302						
Yes	3117	3	3143	33	91 (70–97)	
No	3903	7	3876	63	89 (76–95)	
2019nCoV-301						
Yes	8109	7	3910	34	91 (79–96)	
No	9203	7	4230	29	90 (77–96)	
2019nCoV – 501						
HIV infection	77	10	73	7	-35 (-237, 46)	

	Vaccine group		Placebo group		VE% (95% CI)	Notes
Group	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**		
Age group (years) and comorbidity (confirmed symptomatic COVID-19 disease of any severity (mild, moderate, or severe))						
2019nCoV-302						
18–64, no	2980	6	2971	58	90 (76–96)	
18–64, yes	2087	3	2091	29	90 (66–97)	
≥ 65, no	923	1	905	5	81 (-73–100)	
≥ 65, yes	1030	0	1052	4	100 (-54–100)	
Baseline SARS-CoV-2 status (confirmed symptomatic COVID-19 disease of any severity (mild, moderate, or severe))						
2019nCoV-302						
Regardless of baseline SARS-CoV-2 status	7332	10	7314	97	90 (80, 95)	
Positive SARS-CoV-2 status	312	0	295	1	100 (-3463–100)	
Negative SARS-CoV-2 status	7020	10	7019	96	90 (80–95)	
2019nCoV-301						
Regardless of baseline SARS-CoV-2 status	18 438	15	8740	64	90 (82–94)	
Positive SARS-CoV-2 status	1126	1	599	1	48 (-3995–99)	
Negative SARS-CoV-2 status	17 312	14	8140	63	90 (83–95)	
2019nCoV-501						
Regardless of baseline SARS-CoV-2 status	1939	63	1906	123	50 (32, 63)	
Positive SARS-CoV-2 status	531	12	544	27	55 (11, 77)	
Negative SARS-CoV-2 status	1408	51	1362	96	49 (28, 63)	

	Vaccine group		Placebo group		VE% (95% CI)	Notes
Group	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**		
By SARS-CoV-2 variant						
2019nCoV-302						
Alpha	7020	8	7019	58	86 (71–93)	
Non-Alpha	7020	1	7019	28	96 (74–99)	
2019nCoV-301						
Variants not considered as VOC/VOI	17 312	0	8140	10	100 (81–100)	Key secondary endpoint
Variants considered as VOC/VOI	17 312	6	8140	38	93 (84–97)	Secondary endpoint
Alpha	17 312	4	8140	27	94 (82–98)	Post-hoc analysis

[a] Mean follow-up time at data lock was 92.6 days for clinical study 2019nCoV-302, and 86.8 days for clinical study 2019nCoV-301. Vaccine efficacy analyses were based on the per-protocol efficacy (PP-EFF) analysis set (baseline seronegative participants only) and PP-EFF 2 analysis set (baseline seropositive only or regardless of baseline serostatus). Most analyses were based on the log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age group and pooled region) as fixed effects and robust error variance*(10)*. The Clopper-Pearson model replaced the log-linear model using the modified Poisson regression because few events were observed in at least one of the study vaccine groups (or at least one stratum) and Poisson regression analysis failed to converge. The 95% CIs calculated using the Clopper-Pearson exact binomial method were adjusted for the total surveillance time.

[b] No cases of severe disease in vaccinated group versus 14 cases of severe disease in placebo group (5 cases in 2019nCoV-501, 5 cases in 2019nCoV-302, and 4 cases in 2019nCoV-301.

[c] Any symptomatic COVID-19 disease includes participants that did not meet the case definition for mild, moderate or severe disease but did have some symptoms.

[d] NA – not available at the time of publication

Booster dose studies

Limited data are available on the duration of protection following two doses of NVX-CoV2373. In a phase 2 study*(11)*, a single booster dose of NVX-CoV237 with Matrix-M adjuvant was administered to healthy adults aged 18– 84 years approximately 6 months following their primary two-dose vaccination series. Safety and immunogenicity parameters were assessed, including assays for IgG, neutralizing antibodies (MN_{50}), and hACE2 inhibition against the ancestral SARS-CoV-2 strain and select variants (B.1.351 (beta), B.1.1.7 (alpha), B.1.617.2 (delta) and B.1.1.529 (omicron)). This trial is registered with ClinicalTrials.gov (NCT04368988).

Geometric mean neutralizing antibody titres fell from 1581 on day 14 after dose 2 to 65 after 6 months (a ~25-fold reduction); the implications of this drop in antibody levels for clinical protection are uncertain. Following the booster dose, neutralizing antibody titres increased 4.3-fold compared with the levels 14 days after dose 2 (3.7-fold in adults aged 18–59 years and 4.7-fold in adults aged 60–84 years).

An incremental increase in the incidence of solicited local and systemic reactogenicity events was observed for the booster dose compared with the primary vaccination series. Following the booster, incidence rates of local and systemic reactions were 82.5% (13.4% ≥ grade 3) and 76.5% (15.3% ≥ grade 3), respectively, compared with 70.0% (5.2% ≥ grade 3) and 52.8% (5.6% ≥ grade 3), respectively, following the primary vaccination series. Events were primarily mild or moderate and transient in nature, with a median duration of 1.0 to 2.5 days, depending on the symptom.

Immune responses observed 28 days after the booster dose were compared with those seen 14 days after the primary vaccination series. For the ancestral SARS-CoV-2 strain, serum IgG GMTs increased ~4.7-fold, from 43 905 ELISA units (EU) on day 35 (14 days after dose 2) to 204 367 EU 28 days after the booster dose at 6 months. Neutralization (MN_{50}) assay GMTs showed a similar increase of ~4.1-fold, from 1470 on day 35 to 6023 after the booster dose. A functional hACE2 receptor binding inhibition assay analyzing activity against ancestral and variant strains of SARS-CoV-2 at Day 189 vs Day 217 found 54.4-fold (Ancestral), 21.9-fold (Alpha), 24.5-fold (Beta), 24.4-fold (Delta), and 20.1-fold (Omicron) increases in titers.

Median follow-up after the second dose was 45–64 days in the phase 2 and phase 3 efficacy trials. There are no data on clinical efficacy or effectiveness following a booster dose.

Administration of a booster dose of NVX-CoV2373 approximately 6 months after the primary vaccination series resulted in an incremental increase in reactogenicity and an enhanced immune response. Immune responses following the booster were notably higher than those associated with high levels of efficacy in the phase 3 studies.

Safety

Phase 3 safety findings

The AE profile of NVX-CoV2373 was studied across the clinical development programme. Unsolicited AEs, especially unsolicited related AEs, tended to be reported more frequently in the NVX-CoV2373 group than in the placebo group. Most unsolicited AEs were mild or moderate in severity. Severe AEs and serious AEs were reported infrequently and at similar frequencies between the vaccine and placebo groups; this was also true for AEs leading to discontinuation from the study, medically attended AEs (MAAEs), and AEs of special interest (AESIs). A total of 21 deaths were reported, of which 13 occurred in the NVX-CoV2373 group and 8 in the placebo group. None of the deaths in NVX-CoV2373 recipients were assessed as related to the vaccination.

Overall, solicited local and systemic AEs were more frequent among NVX-CoV2373 recipients than among placebo recipients after each vaccination (Tables 4 and 5). In the NVX-CoV2373 group, the frequency and intensity of solicited local and systemic AEs were greater after the second vaccination than after the first in all studies except study 2019nCoV-501. Most participants in the NVX-CoV2373 group reported grade 1 or grade 2 local and systemic events following each vaccination. The frequency of grade 3 events was relatively low (<10% for local and <15% for systemic AEs), but such events did generally occur more frequently in the NVX-CoV2373 group than in the placebo group. Few participants reported grade 4 events. The most frequent solicited local AEs following each vaccination were tenderness and pain (incidence >20%), with median durations of 2.0 and 1.0 days, respectively. The most frequent solicited systemic AEs following each vaccination were fatigue, headache, and muscle pain (incidence > 20%), which had median durations of 1.0 day following each vaccination. Across the two age strata (18–64 years and ≥65 years), older participants reported a lower frequency and intensity of solicited local and systemic AEs than younger participants. No clinically relevant difference in the reactogenicity profile of NVX-CoV2373 was observed by sex or comorbidity status.

No serious adverse events or anaphylactic events were reported.

Table 4. Summary of adverse events reported across all clinical studies [a]

	Total			Dose 1			Dose 2		
Adverse event category	**NVX-CoV2373 N (%)**	**Placebo N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 N (%)**	**Placebo N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 N (%)**	**Placebo N (%)**	**Risk difference (%, 95% CI)**
Days 0–28 after vaccination									
All ages									
Systemic	15 925 (70)	6153 (47)	21 (20–22)	10 089 (46)	4685 (37)	7 (6–8)	13 334 (64)	3767 (32)	30 (29–31)
Local	17 385 (76)	3788 (29)	45 (44–46)	12 186 (55)	2512 (20)	34 (33–35)	15 300 (74)	2246 (19)	52 (51–53)
18–64 years									
Systemic	NA[b]	NA	NA	9239 (48)	4240 (38)	8 (7–9)	12 205 (67)	3427 (33)	31 (30–32)
Local	NA	NA	NA	11 192 (58)	2296 (21)	36 (35–37)	13 852 (76)	2058 (20)	53.12 (52–54)
≥65 years									
Systemic	NA	NA	NA	850 (32)	445 (30)	1.39 (-2–4)	1129 (47)	340 (25)	21 (18–24)
Local	NA	NA	NA	994 (37)	216 (14)	22.03 (19–25)	1448 (61)	188 (14)	45 (43–48)

	Total			Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 22 805) N (%)**	**Placebo (N = 13 035) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 22 109) N (%)**	**Placebo (N = 12 651) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 20 732) N (%)**	**Placebo (N = 11 834) N (%)**	**Risk difference (%, 95% CI)**
Days 0–7 after vaccination[b]									
Any local (all grades)	17 385 (76)	3788 (29)	45 (44–46)	12 186 (55)	2512 (20)	34 (33–35)	15 300 (74)	2246 (19)	52 (51–53)
Grade 3	NA	NA	NA	244 (1)	31 (0.3)	NA	1268 (6.12)	35 (0.30)	NA
Pain	13 502 (59)	2393 (18)	39 (39–41)	7354 (33)	1390 (11)	21.93 (21.10–22.76)	11 546 (56)	1442 (12)	42 (41–43)
Grade 3	NA	NA	NA	79 (0.4)	8 (0.1)	NA	354 (2)	15 (0.1)	NA
Tenderness	15 978 (70)	2867 (22)	46 (45–47)	10 782 (49)	1922 (15)	32 (31–33)	14 055 (68)	1628 (14)	51 (50–52)
Grade 3	NA	NA	NA	190 (0.9)	21 (0.2)	NA	923 (4)	20 (0.2)	NA
Erythema	1439 (6)	69 (0.5)	5.7 (5–6)	210 (1)	37 (0.3)	0.7 (0.5–0.8)	1287 (6)	35 (0.3)	5.7 (5–6)
Grade 3	NA	NA	NA	4 (0.0)	1 (0.0)	NA	157 (0.76)	2 (0.02)	NA
Swelling	1331 (6)	67 (0.5)	5 (5–6)	188 (0.9)	36 (0.3)	0.6 (0.4–0.7)	1205 (6)	33 (0.3)	5 (5–6)
Grade 3	NA	NA	NA	7 (0.0)	4 (0.0)	NA	98 (0.47)	2 (0.02)	NA
Any systemic (all grades)	15 925 (70)	6153 (47)	21 (20–22)	10 089 (46)	4685 (37)	7 (6–8)	13 334 (64)	3767 (32)	30 (29–31)
Grade 3	NA	NA	NA	507 (2)	248 (2)	NA	2223 (11)	236 (2)	NA
Fever	1216 (5)	148 (1)	4.22 (4–5)	139 (0.6)	90 (0.7)	0.06 (-0.1–0.2)	1091 (5)	61 (0.5)	5 (4–5)

	Total			Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 22 805) N (%)**	**Placebo (N = 13 035) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 22 109) N (%)**	**Placebo (N = 12 651) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 20 732) N (%)**	**Placebo (N = 11 834) N (%)**	**Risk difference (%, 95% CI)**
Grade 3	NA	NA	NA	21 (0.1)	15 (0.1)	NA	76 (0.4)	11 (0.1)	NA
Fatigue	11 181 (49)	3629 (28)	18.95 (18–20)	5289 (24)	2491 (20)	3 (2–4)	9280 (45)	2178 (18.40)	24 (23–25)
Grade 3	NA	NA	NA	259 (1)	119 (1)	NA	1487 (7.17)	133 (1.12)	NA
Headache	10 720 (47)	3829 (29)	16 (15–17)	5311 (24)	2712 (21)	2 (1–3)	8501 (41)	2102 (18)	22 (21–23)
Grade 3	NA	NA	NA	170 (0.8)	86 (0.7)	NA	573 (3)	67 (0.6)	NA
Malaise	8586 (38)	2113 (16)	20 (19–21)	3039 (14)	1317 (10)	2 (2–3)	7270 (35)	1235 (10)	23 (22–24)
Grade 3	NA	NA	NA	160 (0.7)	65 (0.5)	NA	1126 (5)	74 (0.6)	NA
Joint pain	5168 (23)	1351 (10)	11.76 (11–13)	1711 (8)	827 (7)	1 (0.6–2)	4233 (20)	746 (6)	13 (13–14)
Grade 3	NA	NA	NA	71 (0.3)	35 (0.3)	NA	459 (2)	34 (0.3)	NA
Muscle pain	10 802 (47)	2343 (18)	28 (27–29)	4761 (22)	1569 (12)	9 (8–9)	9071 (44)	1243 (11)	31 (30–32)
Grade 3	NA	NA	NA	104 (0.5)	45 (0.4)	NA	904 (4)	46 (0.4)	NA
Nausea or vomiting	3169 (14)	1122 (9)	5 (4–6)	1383 (6)	676 (5)	0.9 (0.4–1)	2194 (11)	584 (5)	5 (5–6)
Grade 3	NA	NA	NA	22 (0.1)	14 (0.1)	NA	41 (0.2)	13 (0.1)	NA

[a] Includes data from clinical studies 2019nCoV-101 (parts 1 and 2), 2019nCoV-501, 2019nCoV-302 and 2019nCoV-301. Data lock dates: 18 December 2020 (101, part 1), 14 December 2020 (101, part 2), 23 February 2021 (501), 15 March 2021 (302), and 01 June 2021 (301). For clinical studies 2019nCoV-101 (parts 1 and 2), only safety data from the placebo and 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant

groups were included in the aggregate safety analysis. Risk difference and its confidence intervals are computed from Mantel-Haenszel standardized risk estimates and 95% normal confidence limits with the stratification by study, while individual group statistics are not adjusted by strata.

[b] NA – not available at the time of publication.

Table 5. Solicited adverse events reported 0–7 days after vaccination across clinical studies, by age group [a, b]

	Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 19 436) N (%)**	**Placebo (N = 11 153) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 18 340) N (%)**	**Placebo (N = 10 488) N (%)**	**Risk difference(%, 95% CI)**
Age group 18–64 years						
Any local (all grades)	11 192 (58)	2296 (21)	36 (35, 37)	13 852 (76)	2058 (20)	53 (52–54)
Grade 3	229 (1)	28 (0.3)	NA[b]	1206 (7)	32 (0.3)	NA
Pain	6846 (35)	1276 (11)	23 (23– 24)	10570 (58)	1320 (13)	43 (42– 44)
Grade 3	374 (2)	66 (0.6)	NA	340 (2)	14 (0.1)	NA
Tenderness	9902 (51)	1752 (16)	33 (32– 34)	12731 (69)	1501 (14)	52 (51– 53)
Grade 3	179 (1)	19 (0.2)	NA	888 (5)	19 (0.2)	NA
Erythema	190 (1)	32 (0.3)	0.7 (0.5– 0.9)	1162 (6)	31 (0.3)	6 (5– 6)
Grade 3	4 (0.02)	1 (<0.01)	NA	148 (0.81)	2 (0.02)	NA
Swelling	170 (0.9)	35 (0.3)	0.6 (0.4– 0.7)	1066 (6)	26 (0.3)	5 (5– 6)
Grade 3	6 (0.0)	4 (0.0)	NA	88 (0.5)	1 (<0.01)	NA

	Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 19 436) N (%)**	**Placebo (N = 11 153) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 18 340) N (%)**	**Placebo (N = 10 488) N (%)**	**Risk difference(%, 95% CI)**
Any systemic (all grades)	9239 (48)	4240 (38)	8 (7–9)	12 205 (67)	3427 (33)	31 (30–32)
Grade 3	466 (2.4)	234 (2.1)	NA	2129 (12)	216 (2)	NA
Fever	121 (0.6)	78 (0.7)	0.1 (-0.1–0.3)	1046 (6)	49 (0.5)	5 (5–6)
Grade 3	19 (0.1)	14 (0.1)	NA	73 (0.4)	9 (0.1)	NA
Fatigue	4855 (25)	2278 (20)	3 (2–4)	8592 (47)	1991 (19)	25 (24–26)
Grade 3	235 (1)	114 (1)	NA	1425 (8)	119 (1)	NA
Headache	4906 (25)	2486 (22)	2 (1–3)	7932 (43)	1930 (18)	23 (22–24)
Grade 3	157 (0.8)	82 (0.7)	NA	555 (3)	64 (0.6)	NA
Malaise	2776 (14)	1202 (11)	3 (2–4)	6766 (37)	1119 (11)	24 (23–25)
Grade 3	145 (0.8)	61 (0.5)	NA	1085 (6)	67 (0.6)	NA
Joint pain	1546 (8)	736 (7)	1 (0.8–2)	3932 (21)	670 (6)	14 (13–15)
Grade 3	65 (0.3)	30 (0.3)	NA	440 (2)	31 (0.3)	NA
Muscle pain	4426 (23)	1419 (13)	9 (8–10)	8440 (46)	1120 (11)	33 (32–34)
Grade 3	101 (0.5)	41 (0.4)	NA	870 (5)	43 (0.4)	NA
Nausea or vomiting	1284 (7)	638 (6)	0.8 (0.3–1)	2068 (11)	542 (5)	6 (5–6)

	Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 19 436) N (%)**	**Placebo (N = 11 153) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 18 340) N (%)**	**Placebo (N = 10 488) N (%)**	**Risk difference(%, 95% CI)**
Grade 3	22 (0.1)	14 (0.1)	NA	39 (0.2)	13 (0.1)	NA
Age group ≥65 years						
Any local (all grades)	994 (37)	216 (14)	22 (19–25)	1448 (61)	188 (14)	45 (43–48)
Grade 3	15 (0. 6)	3 (0.2)	NA	62 (3)	3 (0.2)	NA
Pain	508 (19)	114 (8)	11 (9–13)	976 (41)	122 (9)	30 (28–33)
Grade 3	4 (0.2)	1 (0.1)	NA	14 (0.6)	1 (0.1)	NA
Tenderness	880 (33)	170 (11)	21 (19– 23)	1324 (55)	127 (9)	45 (43–48)
Grade 3	11 (0.4)	2 (0.1)	NA	35 (1)	1 (0.1)	NA
Erythema	20 (0.8)	5 (0.3)	0.4 (-0.1–0.9)	125 (5)	4 (0.3)	5 (4–6)
Grade 3	0	0	NA	9 (0.38)	0	NA
Swelling	18 (0.7)	1 (0.1)	0.6 (0.2–0.9)	139 (6)	7 (0.5)	5 (4–6)
Grade 3	1 (0.0)	0	NA	10 (0.4)	1 (0.1)	NA
Any systemic (all grades)	850 (32)	445 (30)	1 (-1–4)	1129 (47)	340 (25)	21 (18–24)
Grade 3	41 (2)	14 (1)	NA	94 (4)	20 (1)	NA
Fever	18 (0.7)	12 (0.8)	0.03 (-0.5–0.6)	45 (2)	12 (0.9)	1 (0.3–2)

	Dose 1			Dose 2		
Solicited adverse event	**NVX-CoV2373 (N = 19 436) N (%)**	**Placebo (N = 11 153) N (%)**	**Risk difference (%, 95% CI)**	**NVX-CoV2373 (N = 18 340) N (%)**	**Placebo (N = 10 488) N (%)**	**Risk difference(%, 95% CI)**
Grade 3	2 (0.1)	1 (0.1)	NA	3 (0.1)	2 (0.1)	NA
Fatigue	434 (16)	213 (14)	1 (-1–3)	688 (29)	187 (14)	14 (11–16)
Grade 3	24 (0.9)	5 (0.3)	NA	62 (3)	14 (1)	NA
Headache	405 (15)	226 (15)	-0.2 (-2–2)	569 (24)	172 (13)	10 (8–13)
Grade 3	13 (0.5)	4 (0.3)	NA	18 (0.8)	3 (0.2)	NA
Malaise	263 (10)	115 (8)	2 (-0.1–4)	504 (21)	116 (9)	12 (9–14)
Grade 3	15 (0.6)	4 (0.3)	NA	41 (2)	7 (0.5)	NA
Joint pain	165 (6)	91 (6)	0.1 (-2–2)	301 (13)	76 (6)	6 (5–8)
Grade 3	6 (0.2)	5 (0.3)	NA	19 (0.8)	3 (0.2)	NA
Muscle pain	335 (13)	150 (10)	2 (0.1–4)	631 (26)	123 (9)	16 (14–19)
Grade 3	3 (0.1)	4 (0.3)	NA	34 (1)	3 (0.2)	NA
Nausea or vomiting	99 (4)	38 (3)	1 (0.0–2)	126 (5)	42 (3)	2 (0.6–3)
Grade 3	0	0	NA	2 (0.1)	0	NA

[a] Includes data from clinical studies 2019nCoV-101 (parts 1 and 2), 2019nCoV-501, 2019nCoV-302 and 2019nCoV-301. Data lock dates: 18 December 2020 (101, part 1), 14 December 2020 (101, part 2), 23 February 2021 (501), 15 March 2021 (302), and 01 June 2021 (301). For clinical studies 2019nCoV-101 (parts 1 and 2), only safety data from the placebo and 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant groups were included in the aggregate safety analysis. Risk difference and its confidence intervals are computed from Mantel-Haenszel standardized risk estimates and 95% normal confidence limits with the stratification by study, while individual group statistics are not adjusted by strata.

[b] NA – Not available at the time of publication.

Special considerations

Pregnancy

The safety of NVX-CoV2373 in pregnant individuals has not yet been studied. In each study of the clinical development programme, all efforts were made to avoid enrolling pregnant participants. In order to enrol, participants of childbearing age were required agree to use an approved contraceptive method to prevent pregnancy. For participants of childbearing age, a urine pregnancy test was performed at screening and before each vaccination; those with a positive urine pregnancy test at screening were not enrolled, and those with a positive test prior to vaccination were not vaccinated. Participants who became pregnant during the study were followed for the duration of the pregnancy to document the pregnancy outcome.

A total of 137 pregnancies had been reported in the clinical development programme as of 26 October 2021. Of these, 95 women had received NVX-CoV2373 and 42 placebo. Of those who received vaccine, 48 had their last dose of vaccine more than 30 days before their last menstrual period (LMP); for 13 participants the date of LMP was unknown. Thirty-four vaccinated participants became pregnant in the periconception period (the start of the periconception period was defined as 30 days prior to LMP). Of these, six had a live birth, four had a voluntary termination, seven had a spontaneous abortion, 15 are still pregnant, and two outcomes are unknown. For the 42 participants who received placebo, it was unclear when they became pregnant relative to their last dose of placebo. Thirteen participants had a live birth, five had a voluntary termination, four had a spontaneous abortion, and 18 are still pregnant. The rate of spontaneous abortions was reported to be similar to background rates in the populations studied. There were no fetal deaths or stillbirths reported in the clinical development programme.

Post-marketing pregnancy surveillance data are being collected via pregnancy registries.

Breastfeeding

It is unknown whether the vaccine is excreted in human milk.

Paediatric population

A phase 3 expansion trial has been initiated with adolescent participants 12 to <18 years of age (ClinicalTrials.gov Identifier: NCT04611802).

Immunosuppression

No data are currently available regarding the efficacy of NVX-CoV2373 in moderately or severely immunocompromised subjects, but VE may be lower in immunocompromised individuals.

The phase 2 clinical trial in South Africa (2019nCoV-501) *(3)* included 244 medically stable people with HIV infection aged 18 to 64 years (122 in the vaccine group and 122 in the placebo group). A two-dose regimen of NVX-CoV2373, administered 21 days (+7 days) apart, induced less robust immune responses (anti-S protein IgG and neutralizing antibody) in HIV-positive participants than in those who were HIV-negative *(12)*. In participants who were seronegative to SARS-CoV-2 at baseline, anti-S protein IgG immune responses were approximately 2-fold greater in those who were HIV-negative. In those who were seropositive at baseline, antibody responses were comparable. VE against COVID-19 was not assessed because of the limited sample size. The safety profile of NVX-CoV2373 in HIV-positive participants was similar to that seen in HIV-negative participants.

Safety related to vaccine interactions

As part of the phase 3 trial in the United Kingdom, a substudy assessed the safety, immunogenicity and efficacy of NVX-CoV2373 vaccine coadministered with seasonal influenza vaccines *(13)*. Participants were randomized in a 1:1 ratio to receive NVX-CoV2373 ($n = 217$) or placebo ($n = 214$). Together with dose 1, they also received an age-appropriate, licensed influenza vaccine (Quadrivalent influenza vaccine, conjugated (QIVc) for those aged 18–64 years and adjuvanted trivalent vaccine (aTIV) for those aged 65 years or over). Reactogenicity was evaluated in an electronic diary for seven days postvaccination, and participants were monitored for unsolicited AEs, MAAEs, and serious AEs.

Reactogenicity events were more common in the coadministration group and included tenderness (65% vs 53%) or pain (40% vs 30%) at the injection site, fatigue (28% vs 19%), and muscle pain (28% vs 21%). Rates of unsolicited AEs, MAAEs, and SAEs were low and similar between the two groups. Coadministration did not affect the influenza vaccine immune response, but antibody responses to the NVX-CoV2373 vaccine were reduced. Vaccine efficacy against symptomatic COVID-19 (confirmed by polymerase chain reaction) in the sub-study was 88% (95% CI: –0.2%, 98%) while efficacy in the main study was 90% (95% CI: 80%, 96%).

No other data are available on use of the vaccine with concomitant vaccines.

Heterologous vaccine schedules

Two clinical trials have assessed heterologous schedules involving the administration of NVX-CoV2373 after other WHO EUL COVID-19 vaccines as either a second dose (in a heterologous primary series) or a booster dose (following a 2-dose homologous primary series) *(14, 15)*. Compared with homologous schedules involving ChAdOx1-S alone, heterologous schedules involving ChAdOx1-S followed by NVX-CoV2373 induced higher neutralizing antibody concentrations (postvaccination ratios of 2.0 and 3.8 for primary and booster schedules, respectively) and cellular responses. Compared with homologous schedules involving BNT162b2 alone, heterologous schedules involving BNT162b2 followed by NVX-CoV2373 induced lower neutralizing antibody (post-vaccination ratios of 0.3 and 0.4 for primary and booster schedules, respectively) and cellular responses. Heterologous NVX-CoV2373 had a similar reactogenicity compared with homologous schedules. No data are currently available for schedules involving other WHO EUL COVID-19 vaccines after NVX-CoV2373.

Post licensure studies

This vaccine has not been used as yet. Post-marketing studies are expected in the coming months.

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