Safety and efficacy of the Novavax vaccine—a narrative review

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Abstract
Mass vaccination programs are a public health priority for managing the global coronavirus disease (COVID-19) pandemic. The NVX-CoV2373 vaccine is being developed by Novavax. It consists of a SARS-CoV-2 spike glycoprotein subunit (NVX-CoV2373), which has been shown to have structural stability with pH and temperature perturbations, and the saponin-based Matrix-M adjuvant, which is added to enhance the B- and T-cell-mediated immune response. Animal studies in mice, olive baboons, and cynomolgus macaques demonstrated the potential of this vaccine in protecting the respiratory tract against COVID-19. Subsequent phase 1 and 2 trials then confirmed its safety and the dose-sparing potential of Matrix-M. The results led to the use of a low dose (5 μg) of NVX-CoV2373 in phase 3 trials. In a phase 3 trial involving 14,039 participants, the vaccine efficacy rate was 89.7% (prevention of symptomatic infection). Local and systemic adverse events were mild and self-limiting; commonly reported symptoms included injection-site pain and tenderness, headache, myalgia, and fatigue. A subgroup study confirmed the safety and efficacy of co-administering the NVX-CoV2373 vaccine and the seasonal influenza vaccine. Overall, the vaccine has been found to be safe and effective, meeting the minimum vaccine efficacy rate of 50% to be considered for COVID-19 vaccine emergency use listing approval. 

Keywords: Clinical trials, COVID-19, COVID-19 vaccine, immunology

Introduction

The global coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected many lives. As of October 13, 2021, there were 238,521,855 confirmed cases of COVID-19 and 4,863,818 deaths worldwide. Vaccines offer hope for containing this infectious disease, and 6,364,021,792 vaccine doses had been administered as of October 9, 2021 [1]. Currently, the COVID-19 vaccines that have received the World Health Organization’s Emergency Use Listing (EUL) are the Pfizer-BioNTech, Moderna, AstraZeneca, Sinopharm, Sinovac, and Janssen vaccines, which are variously based on mRNA, an adeno-viral vector, or inactivated virus [2]. The NVX-CoV2373 vaccine, produced by Novavax, is a protein-based vaccine that has completed a phase 3 trial, and it is hoped that it will be rolled out shortly. This narrative review summarizes the Novavax vaccine trial findings.

Methods

The PubMed, MEDLINE, SCOPUS, and Google Scholar databases were searched using the search terms ‘COVID-19 vaccine,’ ‘protein subunit vaccine,’ ‘immunisation,’ ‘novavax,’ and ‘NVX-CoV2373’ on October 1, 2021. All relevant studies were included in the review. 

Development of NVX-CoV2373

NVX-CoV2373 is a SARS-CoV-2 spike glycoprotein subunit derived from the full-length spike (S) protein. The SARS-CoV-2 S gene that encodes the 1,273 amino acid S protein was mutated at the native furin cleavage site (RRAR to QQAD) to develop the full-length BV2365 variant, which is protease resistant. Two additional proline substitutions, at positions K986P and V987P, were introduced to provide further stability in the double mutant NVX-CoV2373. These genes were then codon-optimized...
for expression in Sf9 (Spodoptera frugiperda) cells. When purified SARS-CoV-2 (wild-type), BV2365, and NVX-CoV2373 proteins were compared in 48-hour tests involving incubation at pH extremes (pH 4 and pH 9), prolonged agitation, freeze/thaw cycles, or elevated temperatures (25 °C and 37 °C). Compared to the other proteins, NVX-CoV2373 was found to have significantly greater structural stability, and its human angiotensin I-converting enzyme-2 (hACE2) receptor-binding activity was minimally affected after these stressors [3].

The Novavax vaccine is a combination of NVX-CoV2373 and the saponin-based Matrix-M adjuvant. Subcutaneous administration of Matrix-M in the absence of an antigen has been shown to promote leukocyte recruitment to the nearby lymph nodes and spleen in mice, with improved activation and maturation of immune cells, especially dendritic cells, to enhance uptake, processing, and presentation of antigens [4]. Supplementing subunit vaccines with Matrix-M has been shown to enhance B- and T-cell immune stimulation in response to the vaccine, with the advantage of dose-sparing potential [5]. The published studies on the development of NVX-CoV2373 are shown in Figure 1.

Preclinical animal studies

![Figure 1. Stages of development of NVX-CoV2373 vaccine.](http://www.antpublisher.com/index.php/APT/index)
In terms of immunogenicity, enzyme-linked immunosorbent assay (ELISA) results showed that the anti-S IgG geometric mean fold rises in all the adjuvanted regimens exceeded those in the non-adjuvanted regimens by 10 times. This further increased by a factor of 8 a week after the second dose, doubling again by 14 days and exceeding levels found in the convalescent serum of hospitalized patients with COVID-19. The immunogenicity resulting from two doses of the 5 and 25 μg vaccines with adjuvant was similar, confirming the dose-sparing capability of Matrix-M1. The adjuvanted regimens also induced effective polyfunctional CD4+ T-cell responses and associated TNF-α, IFN-γ, and IL-2 production when cells were stimulated by S protein. The Th1-type response was preferred over the Th2-type response, and there was minimal IL-5 and IL-13 cytokine production [7].

**Phase 2 clinical trials**

After the safety and immunogenicity data were confirmed for up to two weeks after the second dose (day 35), the next stage of the phase 2 trial was a randomized study. This was conducted between August 24 and September 25, 2020, and involved 1,288 randomized participants at 17 sites in the United States and Australia. There were two groups based on age: 18–59 years and 60–84 years. NVX-CoV2373 doses were all adjuvanted with Matrix-M1. Participants received either one or two intramuscular doses of 5 and 25 μg NVX-CoV2373 or placebo three weeks apart. Regardless of age, solicited local adverse events were more common in the participants who received NVX-CoV2373 compared to placebo; they were mostly self-limiting tenderness (up to 59%) and pain (up to 38%). Adverse events were more likely in younger participants, with the higher dose, and after dose two. In terms of systemic symptoms, muscle pain was the most frequent symptom (20%). This was also observed in the placebo group after one dose, in which the symptoms were mainly grade 1 and short lasting. Fever occurred in less than 2% of the vaccine recipients. After dose two, the most common systemic symptoms were fatigue (43%), muscle pain (41%), headache (34%), and malaise (30%); again, these were low-grade, self-limiting symptoms regardless of age. Both doses of NVX-CoV2373 induced anti-S IgG GMTs and neutralizing antibodies, exceeding the levels found in convalescent sera of outpatients and hospitalized patients with COVID-19. Overall, this demonstrated that the administration of NVX-CoV2373 induced high immunogenicity and that it was well tolerated by younger and older people. Thus, 5 μg NVX-CoV2373 progressed to phase 2a/b and phase 3 studies [8].

A separate phase 2 trial was conducted in South Africa between August 17 and November 25, 2020, with 2,864 randomized seronegative participants at 16 sites. There were two groups: human immunodeficiency virus (HIV)-negative participants 18–84 years old and HIV-positive participants 18–64 years old who were medically well. Participants received either two doses of 5 μg NVX-CoV2373 or placebo three weeks apart.
In both groups, solicited local adverse events were more common in those who received NVX-CoV2373 compared to placebo, without any significant difference in incidence after the first or second dose. The duration of local adverse events was slightly longer after dose two but was within three days. Severe local adverse events were uncommon but were reported more after dose two in vaccine recipients compared to placebo recipients (4% vs 1%). Similarly, reported systemic symptoms were more common in those who received NVX-CoV2373 compared to placebo. Headache, muscle pain, and fatigue were the most frequent symptoms, lasting slightly longer after dose two.

No differences in reactogenicity were found between the HIV-negative and HIV-positive groups, although the latter sample size was small. Symptomatic COVID-19 infections occurred in 15 participants who were vaccinated and in 29 participants who received placebo, corresponding to a vaccine efficacy of 49.4%. The B.1.351 variant was confirmed in 38 (93%) of the 41 samples sent for whole-genome sequencing. Post hoc analysis identified a vaccine efficacy of 43.0% against the B.1.351 variant compared to placebo. Headache, muscle pain, and fatigue were the most frequent symptoms, lasting slightly longer after dose two.

The likelihood of severe systemic reactions was increased more than twofold in the co-vaccinated group (70.1%) than in the NVX-CoV2373 alone group (57.6%) and in the influenza vaccine (co-administered with placebo) group (39.4%). Systemic reactions were also more common in those co-vaccinated (60.1%) than in the NVX-CoV2373 alone group (45.7%). Commonly reported systemic reactions were myalgia, fatigue, and fever, which were mostly mild and self-limiting. The likelihood of severe systemic reactions was increased more than twofold in the co-vaccinated group compared to the NVX-CoV2373 alone group (2.9% vs 1.3%). However, there were no differences in the frequency of all adverse events between the co-vaccinated group and the NVX-CoV2373 alone group (18.4% vs 17.6%).

More importantly, the immunogenicity of NVX-CoV2373 was not affected by co-administration with the seasonal influenza vaccine (87.5% vs 89.7% in the main study).

Conclusion

The NVX-CoV2373 vaccine phase 3 trial demonstrated its safety and efficacy. The vaccine met the minimum vaccine efficacy rate of 50% to be considered for COVID-19 vaccine EUL approval. Adverse events were mild and self-limiting, occurring more frequently in younger people and after the second dose. Co-administration of this vaccine with the seasonal influenza vaccine is a practical approach...
for reaching population groups at high risk of developing complications from viral respiratory infections.

**Declarations**

**Authors’ contributions:** Choo SZL and Teo SP were involved in conception of the work, acquisition, analysis and interpretation of data, as well as drafting and finalizing the manuscript.

**Availability of data and materials:** Not applicable.

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**Ethical approval and consent to participate:** Not applicable.

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