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**Safety and efficacy of the Novavax vaccine – Narrative review**

Novavax safety and efficacy

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**Abstract**

Mass vaccination programmes are a public health priority to manage the global COVID-19 pandemic. NVX-CoV2373 is a SARS-CoV-2 spike glycoprotein subunit vaccine, which was shown to have structural stability with pH and temperature perturbations. The Novavax vaccine is a combination of NVX-CoV2373 and the saponin-based Matrix M adjuvant, added to enhance B and T-cell immune stimulation. Animal studies in mice, olive baboons and cynomolgus macaques demonstrated the potential of this vaccine in protecting the respiratory tract against COVID-19 infection. The Phase 1 and 2 trials confirmed the safety of the Novavax vaccine and the dose-sparing potential of Matrix M. This confirmed the use of the lower dose (5μg) of NVX-CoV2373 for Phase 3 trials. The Phase 3 trial of 14039 participants identified a vaccine efficacy rate of 89.7% in preventing symptomatic infections. Local and systemic adverse events were mild and self-limiting, with commonly reported symptoms as injection-site pain and tenderness, headache, myalgia and fatigue. A subgroup study confirms the safety and efficacy of co-administration of the Novavax vaccine with seasonal influenza immunization. Overall, the Novavax vaccine shows great potential in contributing to the immunization approaches to managing the pandemic.

**Keywords**

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

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**Introduction**

The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected many lives due to the complications caused by COVID-19 disease. As of 13th October 2021, there were 238,521,855 confirmed cases of COVID-19, with 4,863,818 deaths worldwide. Vaccines offer hope to contain this infectious disease, with 6,364,021,792 vaccine doses administered as of 9th October 2021 [1].Currently, COVID-19 vaccines that have received World Health Organisation Emergency Use Listing (EUL) are the Pfizer-BioNTech, Moderna, AstraZeneca, Sinopharm, Sinovac and Janssen vaccines, which are from the mRNA, adenoviral vector and inactivated virus vaccine platforms [2]. The Novavax vaccine, NVX-CoV2373, is a protein-based vaccine that has completed phase 3 trials. This narrative review summarises the trial findings of the Novavax vaccine, which is hoped to be rolled out in the near future.

**Methods**

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

**Development of NVX-CoV2373**

NVX-CoV2373 is a SARS-CoV2 spike glycoprotein subunit vaccine developed from the full-length spike (S) protein. The SARS-CoV-2 S gene encoding the 1273 amino acid spike protein was mutated at the native furin cleavage site (RRAR to QQAQ) to develop the full-length BV2365 variant, which is protease resistant. Two proline (2P) substitutions at positions K986P and V987P were additionally 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 pH9), prolonged agitation, freeze/thaw cycles or elevated temperatures (25 and 37°C), the NVX-CoV2373 proteins had significantly greater structural stability with minimal effect on hACE2 receptor binding after these stressors [3].

The Novavax vaccine is a combination of NVX-CoV2373 as well as the saponin-based Matrix M adjuvant. Subcutaneous administration of Matrix-M in the absence of an antigen has been shown to promote leucocyte recruitment to local draining lymph nodes and the spleen in mice, with improved activation and maturation of immune cells, especially dendritic cells to enhance the uptake, processing and presentation of antigens [4]. The addition of Matrix M adjuvant to subunit vaccines has been shown to enhance both B and T-cell immune stimulation in response to the vaccine, with the advantage of dose-sparing potential [5].

**Animal Studies**

The immunogenicity of NVX-CoV2373 (0.01μg, 0.1μg, 1μg and 10μg doses) with 5 μg Matrix M adjuvant in a single priming dose and a prime/boost regimen 14 days apart was evaluated in mice. This study showed that in mice, at least 0.1μg doses were required to induce anti-S IgG titres by 21 days. For all doses tested, a prime/boost regimen induced significantly elevated anti-S IgG titres at least 7 days after the booster dose. This was enhanced further with the addition of Matrix-M adjuvant (compared to 10μg NVX-CoV2373 alone), with a potential for a tenfold or greater dose sparing effect. Across all dose levels, a prime boost approach of NVX-CoV2373/Matrix-M induced high titre antibodies which blocked hACE2 receptor binding to S-protein and neutralized the cytopathic effect of SARS-CoV-2 on Vero E6 cells.

The immunized mice were then challenged with 105 plaque forming units(pfu)/mouse of SARS-CoV-2 (WA1 strain). While the prime-only mice immunized with NVX-CoV2373/Matrix-M had a dose-dependent reduction in virus titre, with no detectable virus in the 10μg dose, the prime/boost immunization resulted in undetectable lung virus loads at NVX-COV2373 doses of at least 0.1μg. The viral load suppression correlated with protection from weight loss after infection and inflammation in lung histopathology. Cell mediated immune responses were also elicited with a higher proportion of multifunctional phenotypes within both CD4+ and CD8+ T-cells, with corresponding increased production of IFN-γ, TNF-α, and IL-2 cytokines. These findings in mice were replicated in olive baboons, immunized with a dose range of 1μg, 5μg and 25μg of NVX-COV2373 with 50μg Matrix-M adjuvant in two doses 21-days apart [3].

Using a non-human primate model, cynomolgus macaques at least 3 years old which received 2.5 μg, 5 μg or 25μg NVX-COV2373 with 25μg or 50μg Matrix-M adjuvants induced anti-S IgG antibodies at day 21 after a single dose. This increased significantly two weeks following the booster dose with anti-S IgG titres surpassing convalescent human serum by 6.9 to 14.2 times. There was a correspondingly similar increase for the hACE2 receptor inhibition titres and SARS-CoV-2 GMT neutralization antibody titres. When the macaques were challenged with SARS-CoV-2 virus in the upper and lower airways, the placebo recipients had an average of 9131 sgRNA copies/mL in bronchioalveolar lavage two days post-challenge; as opposed to no detectable sgRNA in the immunized group. The control animals also had moderate to severe inflammation of the bronchi and alveoli, with little or no inflammation in immunized macaques 7 days post-challenge. This demonstrates the potential of NVX-CoV2373 to protect the upper respiratory tract against viral replication, and the lower respiratory tract against pulmonary disease that could be tested in human trials [6].

**Phase 1-2 Trial**

The phase 1-2 trial recruited 131 healthy adults aged 18 to 59 years old who received two intramuscular injections 21 days apart. The participants were randomly assigned into five groups; placebo doses, 5μg NVX-CoV2373 doses with Matrix-M1, 25μg doses NVX-CoV2373 doses with Matrix-M1, 25μg doses NVX-CoV2373 doses without Matrix-M1, and a single dose of 25μg NVX-CoV2373 doses with Matrix-M1 followed by a single dose of placebo. This study was performed at two Australian study sites (Nucleus Network, Herston, Queensland, and Melbourne, Victoria). In terms of reactogenicity, the majority of participants had absent or mild local and systemic side effects after the first and second dose in all five groups. There were eight participants (one or two per group) who had severe systemic events after the second dose, the most common being joint pain and fatigue, which was self-limiting. In terms of immunogenicity outcomes, the ELISA anti-spike IgG geometric mean fold rises (GMFRs) in all adjuvanted regimens exceeded those without adjuvant by 10 times. This further increased by a factor of 8 a week after the second dose, doubling again by 14 days and exceeding those in convalescent serum from patients hospitalized with Covid-19. The responses in the two dose 5μg and 25μg adjuvanted vaccines were similar, confirming adjuvant dose sparing with Matrix-M1. There were also effective polyfunctional CD4+ T-cell responses with adjuvanted regimens with associated IFN-γ, IL-2, and TNF-α production during spike protein stimulation; with a strong bias towards Th1 phenotype and minimal Th2 responses (IL-5 and IL-13 cytokines) [7].

**Phase 2 Trials**

After confirming safety and immunogenicity data up to day 35 (14 days after the second dose), the phase 2 trial randomized 1288 participants between 24th August 2020 and 25th September 2020 at 17 sites in Australia and the United States. There were two age groups, 18 to 59 years and 60 to 84 years. Subsequent NVX-CoV2373 doses were all adjuvanted with Matrix-M1. Participants received either one or two intramuscular doses of 5μg and 25μg NVX-CoV2373 or placebo 21 days apart. Across both age groups, solicited local adverse events were more common in the NVX-CoV2373 than in placebo group; mostly self-limiting tenderness (up to 59%) and pain (up to 38%). This was more likely in younger participants, with the higher dose, and after the second dose. For systemic symptoms, muscle pain was the most commonly reported (20%). This was similar to the placebo group after the first dose, predominantly Grade 1 and of short duration. Fever was reported in less than 2% of vaccine recipients. After the second dose, the most common systemic adverse events were fatigue (43%), muscle pain (41%), headache (34%) and malaise (30%); again, these were low grade and self-limiting across both age groups. In terms of neutralizing antibodies, both doses of NVX-COV2372 induced anti-spike protein binding IgG geometric mean titres (GMTs) and neutralizing antibody responses, which exceeded those of convalescent sera for outpatient and hospitalized COVID-19 patients. Overall, this demonstrated that NVX-CCoV2373 was highly immunogenic and well-tolerated in younger and older participants, supporting progressing use of the 5μg NVX-CoV2373  in phase 2a/b and phase 3 studies [8].

A separate phase 2 trial in South Africa randomized 2864 seronegative participants between 17th August 2020 and 25th November 2020 at 16 sites. There were two groups, human immunodeficiency virus (HIV)-negative adults between ages of 18 and 84 years and medically stable HIV-positive participants between ages 18 and 64 years. Participants received either two doses of the 5μg  NVX-CoV2373 or placebo 21 days apart. In both groups, solicited local adverse events were more common in the  NVX-CoV2373 than in the placebo group, with a similar incidence rate after the first and second doses. The duration of local adverse events was slightly longer after the second dose but still generally within 3 days. Severe local adverse events were infrequent but occurred more often after the second dose in the vaccine group than in the placebo group (4% vs. 1%). Similarly, solicited systemic adverse events were more common in the NVX-CoV2373 than in the placebo group with headache, muscle pain and fatigue most commonly reported, lasting slightly longer after the second dose. There were no differences in reactogenicity found between the HIV-negative and HIV-positive group, although the latter sample size was small. Symptomatic Covid-19 was observed in 15 participants in the vaccine group versus 29 participants in the placebo group corresponding to a vaccine efficacy of 49.4%. B.1.351 variant was identified in 38 (93%) of the 41 samples sent for whole-genome sequencing. Post hoc analysis identified a vaccine efficacy of 43.0% against B.1.351 variant [9].

**Phase 3 Trial**

The phase 3 trial was conducted across 33 sites in the United Kingdom with 14,039 participants aged between 18 and 84 years randomised between 28th September 2020 and 29th November 2020. There were 27.9% participants who were 65 years of age or older, while 44.6% had coexisting illnesses. Similar to the phase 2 trials, solicited local adverse events were reported more frequently in the vaccine group and were more commonly reported after the second dose compared to the first (79.6% vs. 57.6%). The most commonly reported local adverse events were injection-site pain and tenderness, which were mostly mild to moderate severity and short-lived (< 3 days). Solicited local adverse events were more common among younger vaccine recipients compared to the older recipients (65 years and above). Solicited systemic adverse events were more frequent in the vaccine group than placebo group after the first (45.7% vs. 36.3%) and second doses (64.0% vs 30.0%). The most commonly reported solicited systemic adverse events were headache, muscle pain and fatigue, with most events being grade 1 or 2, and a short mean duration of less than 2 days. Systemic adverse events are more commonly reported in younger vaccine recipients, with Grade 4 systemic adverse events reported in 3 vaccine recipients. Two participants reported grade 4 fever (>40 C); one after the first dose and another after the second dose. Myocarditis was reported in a vaccine recipient three days after the second dose and fully recovered after 2 days of hospitalisation [10].

Of the 14,039 participants, 10 had symptomatic Covid-19 infections at least 7 days after the second dose in the vaccine group compared to 96 in the placebo group, equating to an efficacy rate of 89.7%. The 10 participants from the vaccine group were all aged 65 years and older. Severe Covid-19 disease occurred in 5 participants, who were all from the placebo group. There were two Covid-19 deaths in this study, one from the vaccine group, and another from the placebo group. The death from the vaccine group developed Covid-19 symptoms 7 days after the first dose and passed away 8 days later [10].

There were several limitations to this trial. The study was performed in the United Kingdom, with the majority (94.5%) of participants being white. It is unclear whether these efficacy findings could be extrapolated to other ethnic groups. The study also excluded pregnant ladies, those below age 18 years, people receiving immunosuppressants or those with immunodeficiency, thus further studies are required to assess the safety and efficacy of NVX-CoV2373 in these groups. The trial was also conducted when the B.1.351 (Alpha) variant was prevalent, while efficacy of this vaccine on the B.1.617.2  (Delta) variant, currently causing outbreaks in many parts of the world, would be more relevant.

A subgroup study of this phase 3 trial was performed for the first 400 participants meeting the inclusion criteria without contraindications to the influenza vaccine. After randomization to NVX-CoV2373 or placebo, the sub-study participants received an open-label influenza vaccine with their first dose. Compared to the main study, the subgroup participants were younger and had fewer comorbidities. Local reactions were more prevalent in the co-vaccinated group (70.1%), compared to 57.6% in the NVX-CoV2373 alone group and 39.4% in the influenza vaccine (co-administered with placebo) group. Systemic reactions were also more common in those co-vaccinated, 60.1% compared to 45.7% in the NVX-CoV2373 alone group. 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 two-fold 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 efficacy of NVX-CoV2373 was not affected by the co-administration with seasonal influenza vaccine (87.5% vs 89.7% in the main study). This supports the potential co-administration of COVID-19 and the seasonal influenza vaccine, particularly for at-risk groups, such as older people, pregnancy and multiple comorbidities [11].

**Limitations**

The trial evaluated vaccine efficacy predominantly with the B.1.351 (Alpha) variant, which is hoped to be similar against the B.1.617.2 (Delta) variant, the main variant of concern causing outbreaks in many parts of the world. Long-term adverse events from the vaccine may not have

been identified during the trial, which may only become obvious during post-marketing safety surveillance.

**Conclusion**

The Phase 3 trial for the NVX-CoV2373 vaccine demonstrated its safety and efficacy was comparable to the currently available mRNA and viral vector vaccines. Adverse events were mild and self-limiting, occurring more with younger people and after the second dose. Co-administration of this vaccine with seasonal influenza immunization is a practical approach to reach population groups at high risk of developing complications from viral respiratory infections.

**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

**Financial Support and Sponsorship**

Not applicable

**Conflicts of Interest**

All authors declared that there are no conflicts of interest

**Ethical Approval and Informed Consent**

Not applicable

**Consent for Publication**

Not Applicable

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