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Editorial: First Approval of the Protein-Based Adjuvanted Nuvaxovid (NVX-CoV2373) Novavax Vaccine for SARS-CoV-2 Could Increase Vaccine Uptake and Provide Immune Protection from Viral Variants

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None declared

Abstract

The Nuvaxovid™ (NVX-CoV2373) Novavax vaccine is a recombinant spike (S) protein nanoparticle vaccine combined with the Matrix-M adjuvant. On December 20, 2021, the European Commission of the European Union (EU) granted conditional marketing authorization for the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine, following recommendations from the European Medicines Agency (EMA). On February 3, 2022, this vaccine was granted conditional marketing authorization (CMA) in Great Britain by the Medicines and Healthcare Products Regulatory Agency (MHRA) for use in individuals ≥18 years. The two vaccine components elicit both B-lymphocyte and T-lymphocyte immune responses to the S protein of SARS-CoV-2. The full-length S protein in this vaccine has common epitopes that could protect against all the SARS-CoV-2 viral variants. Also, the vaccine is stable and has a shelf life of 9 months when stored at standard refrigerated temperatures of between 2-8°C. This Editorial aims to present an update on the first approval of a protein-based adjuvanted vaccine for SARS-CoV-2, Nuvaxovid (NVX-CoV2373) from Novavax, and why it is such a significant development at this time.

Keywords:

Editorial • SARS-CoV-2 • COVID-19 • Spike Protein, SARS-CoV-2 • Vaccin

The development, clinical evaluation, regulatory approvals, and vaccination programs for messenger RNA (mRNA) and viral vector-based vaccines to SARS-CoV-2 have rapidly progressed during the past two years [1,2]. Emergency use authorization (EUA) and full regulatory approvals for novel vaccines in 2020 and 2021 resulted in global vaccination programs that have reduced the severity of COVID-19, hospitalizations, and patient mortality [3,4].

However, the rapidity of SARS-CoV-2 vaccine development and reported rare side effects from these novel vaccines, particularly mRNA vaccines, have resulted in concerns that continue to reduce vaccine uptake [5]. Although vaccine-associated adverse events associated with the mRNA vaccines for SARS-CoV-2 are extremely rare, complications such as myocarditis and vaccine-induced immune thrombotic thrombocytopenia (VITT) continue to be reported in the medical literature and popular press [6-9]. Therefore, it is surprising that discovery and development programs were not established earlier in the COVID-19 pandemic to produce more conventional protein-based vaccines.

Nuvaxovid™ (NVX-CoV2373) (Novavax Inc., Gaithersburg, MD, USA) is the first recombinant protein-based vaccine to SARS-CoV-2, combined with an adjuvant, to receive regulatory

approval, currently in Great Britain and the European Union (EU) [10,11]. NVX-CoV2373 is a recombinant spike (S) protein nanoparticle vaccine combined with the Matrix-M adjuvant [11,12]. Preclinical studies have shown that the NVX-CoV2373 SARS-CoV-2 vaccine consists of full-length, stabilized, prefusion, recombinant S protein components combined with a saponin-based adjuvant, Matrix-M [12]. The two vaccine components elicit both B-lymphocyte and T-lymphocyte immune responses to the SARS-CoV-2 S protein, including viral neutralizing antibodies [12,13]. Also, the full-length S protein in this vaccine has common epitopes that could protect against all the SARS-CoV-2 viral variants [12,13].

Each multidose vial of Nuvaxovid™ contains ten 0.5 ml vaccine doses, and each 0.5 ml dose contains 5 micrograms of recombinant SARS-CoV-2 S protein with Matrix-M adjuvant [13]. The adjuvant consists of 42.5 micrograms of Fraction-A and 7.5 micrograms of Fraction-C of *Quillaja saponaria* (Molina) extract [13]. Recombinant SARS-CoV-2 S protein is produced by recombinant DNA technology with a baculovirus expression system in an insect cell line derived from *Spodoptera frugiperda*-derived Sf9 cells (iPLB-Sf21-AE) [13]. Importantly, the vaccine is stable and has a shelf life of 9 months when stored at standard refrigerated temperatures of between 2-8°C [13].

On December 20, 2021, the European Commission of the European Union (EU) granted conditional marketing authorization for the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine, following recommendations from the European Medicines Agency (EMA) [10]. On February 3, 2022, the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine was granted conditional marketing authorization (CMA) in Great Britain for use in individuals ≥18 years by the Medicines and Healthcare Products Regulatory Agency (MHRA) [11]. Currently, Nuvaxovid™ is the fifth SARS-CoV-2 vaccine authorized in Europe, in addition to vaccines from Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, and Janssen Pharmaceutica NV. However, the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine is the first protein-based vaccine authorized as a SARS-CoV-2 vaccine [10,11]. This vaccine has several differences from current vaccines, which may be of benefit now that SARS-CoV-2 is endemic in several countries and continues to develop mutations in the S protein leading to variants with different degrees of infectivity and pathogenicity [10,11].

Authorization for the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine was granted based on data from two ongoing phase 3 clinical trials [14,15]. The results of the first phase 3 randomized, blinded, placebo-controlled trial conducted at 33 sites in the UK were published in September 2021 (EudraCT number, 2020-004123-16) [14]. The study included 14,039 adults between 18-84 years in a 1:1 ratio who were negative for SARS-CoV-2 infection at baseline and received two 5 µg intramuscular doses of NVX-CoV2373 or placebo, 21 days apart [14]. The primary efficacy endpoint was confirmed mild, moderate, or severe SARS-CoV-2 infection, commencing at least seven days after the second vaccination dose [14]. SARS-CoV-2 infection occurred in 10 participants in the vaccinated group and 96 participants in the placebo group [14]. The vaccine efficacy was 89.7% (95% CI, 80.2-94.6) [14]. No hospitalizations or deaths occurred in the symptomatic ten cases in the vaccine group, but five cases of severe COVID-19 occurred in the placebo group [14]. Post hoc analysis showed vaccine efficacy of 86.3% (95% CI, 71.3-93.5) for the B.1.1.7 (alpha) SARS-CoV-2 variant, and 96.4% (95% CI, 73.8-99.5) for the non-B.1.1.7 SARS-CoV-2 variants [14]. Mild, transient injection site reactions were noted [14]. This study showed that a two-dose regimen of Nuvaxovid™ (NVX-CoV2373) Novavax vaccine in adults provided 89.7% protection against SARS-CoV-2 infection, with high efficacy against the B.1.1.7 variant, and a good safety profile [14].

In February 2022, the results from the second key phase 3 study on the safety and efficacy of the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine were published, the PREVENT-19 (PRE-fusion protein subunit Vaccine Efficacy Novavax Trial | COVID-19) study (NCT04611802) [15]. Between December 27, 2020, and February 18, 2021, the PREVENT-19 phase 3, randomized, blinded, placebo-controlled trial enrolled 29,949 participants from Mexico and the US to evaluate the efficacy and safety of NVX-CoV2373 in

adults ≥18 years who had not had previous SARS-CoV-2 infection [15]. The trial participants were randomized (in a 2:1 ratio) to receive two doses of NVX-CoV2373 or placebo at a 21-day interval [15]. Vaccine efficacy was determined by reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection occurring at least seven days after the second vaccine dose [15]. Vaccine efficacy against moderate to severe COVID-19 and against different SARS-CoV-2 variants was also evaluated [15]. During three months, there were 77 confirmed cases of COVID-19, 14 in vaccine recipients, and 63 in placebo recipients with a vaccine efficacy of 90.4% (95% CI, 82.9-94.6; $P < 0.001$) [15]. There were ten moderate COVID-19 cases, and four severe COVID-19 cases in the placebo recipients, with a vaccine efficacy against moderate to severe COVID-19 of 100% (95% CI, 87.0-100) [15]. Most sequenced viral genomes were variants of concern (VOC) or variants of interest (VOI), with 89% B.1.1.7 (alpha), and vaccine efficacy against any VOC or VOI was 92.6% (95% CI, 83.646.7) [15]. At ≤2 days, the most frequently reported local adverse event was tenderness at the injection site, with a median duration of ≤2 days [15]. The most commonly reported events were headache, myalgia, fatigue, and malaise, which were reported more frequently in the NVX-CoV2373 recipients after the second injection, and lasted ≤1 day [15]. No severe systemic adverse events of coagulation abnormalities were reported in individuals receiving the NVX-CoV2373 vaccine [15].

There are several important considerations regarding this new protein-based and adjuvanted vaccine to SARS-CoV-2. First, the two vaccine components elicit both B-lymphocyte and T-lymphocyte immune responses to the SARS-CoV-2 S protein, including viral neutralizing antibodies [12,13]. Also, the rapid and large-scale production of the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine is possible and was planned long before regulatory approval [16]. SARS-CoV-2 vaccine boosters have begun in several countries, and these programs will require increased vaccine supplies that can be easily stored and transported. For example, in the UK, the elderly, healthcare workers, and the clinically vulnerable will receive a second booster, or fourth vaccine, from March 2022. Everyone will be entitled to a further autumn vaccine booster, supported by the UK Vaccines Taskforce [16]. Also, vaccine stability during refrigeration could facilitate the inclusion of the Nuvaxovid™ (NVX-CoV2373) Novavax vaccine in the established routine winter influenza vaccine programs in several countries, with an expected high population uptake [16].

The high rates of lack of vaccine uptake in some countries and by some ethnic groups, promoted by misinformation regarding mRNA vaccines and exaggeration of vaccine-associated adverse events, may be overcome by the availability of a more traditionally produced protein-based vaccine. A further important consideration is that this vaccine may be more acceptable to pregnant women, as the Nuvaxovid™ (NVX-CoV2373) Novavax

vaccine uses similar technology to both pertussis and influenza vaccines that pregnant women have received routinely for several years. Finally, the approval of diverse vaccines that may elicit varied immune responses to the SARS-CoV-2 will facilitate studies on vaccine heterology and the identification of the most effective and cost-effective vaccine regimens [17].

Conclusions

Effective global vaccination programs to prevent or control the severity of COVID-19 are limited by failure to supply enough

vaccine doses, the emergence of new variants of concern, and the reduced effectiveness of available vaccines over time, that require regular booster vaccinations. Compliance with available vaccination programs has been affected by concerns regarding the safety of novel vaccines. The recent and anticipated regulatory approvals of the Nuvaxovid™ (NVX-CoV2373) Novavax protein-based and adjuvanted vaccine to SARS-CoV-2 provide some hope during the COVID-19 pandemic. Data from studies on heterologous vaccines, including protein-based adjuvanted vaccines, may lead to improved cellular and humoral immune responses without significant vaccine-associated adverse reactions while improving global vaccine availability.

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