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SYNOPSIS

Review of "Safety and Efficacy of NVX-CoV2373 COVID-19 Vaccine"

07/08/2021

Article citation: Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 covid-19 vaccine. N Engl J Med. 2021 Jun 30 [Epub ahead of print]. Available from: https://doi.org/10.1056/nejmoa2107659

One-minute summary

- The authors report findings of a phase 3, international, randomized, observer-blind, placebo-controlled trial to evaluate the efficacy and safety of NVX-CoV2373 (Novavax). This vaccine is a recombinant nanoparticle vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that contains the full-length spike glycoprotein of the prototype strain plus Matrix-M adjuvant. It is also referred to as a "protein subunit" or protein-based, adjuvanted vaccine.

- The trial was conducted at 33 sites in the United Kingdom. Participants were enrolled from September 28 to November 28, 2020 during which the B.1.1.7 (alpha) variant was circulating. **Eligible patients were non-pregnant adults between 18 to 84 years of age who were healthy or had stable chronic medical conditions (e.g., human immunodeficiency virus, cardiac and respiratory disease).** Individuals with a history of documented COVID-19, treatment with immunosuppressive therapy or diagnosis of immunodeficient condition were excluded.

- Participants were randomly assigned 1:1 to receive two 5-µg intramuscular doses of Novavax (n=7,020) or saline placebo (n=7,019) given 21 days apart. Randomization was stratified by trial site and age (< 65 years or ≥ 65 years). The primary outcomes were vaccine efficacy against the **first occurrence of virologically confirmed symptomatic mild, moderate or severe COVID-19 with onset ≥ 7 days after the second dose** among participants who were seronegative at baseline. Virologic confirmation was via polymerase chain reaction (PCR) assay.

- **Overall vaccine efficacy was 89.7% (95% confidence interval [CI] 80.2-94.6).** Vaccine efficacy against the alpha variant was 86.3% (95% CI: 71.3-93.5) and 96.4% (95% CI: 73.8-99.5) against non-alpha variants.

- There were more adverse events in vaccine recipients than in the placebo group, more commonly after dose two; most were mild to moderate severity and of short duration. The incidence of serious adverse events was similar between groups.

Additional information

Per-protocol Efficacy Population (N=14,039):

- The per-protocol efficacy population (used in the primary analysis) included 7,020 participants in the vaccine group and 7,019 in the placebo group; 48.4% were women, 27.9% ≥ 65 years old and the median age was 56. The demographic and clinical characteristics of the participants were well balanced between the two groups.

- There were 10 breakthrough symptomatic PCR confirmed COVID-19 infections in vaccine recipients (onset ≥ 7 days after second dose); eight were caused by the alpha variant, one was caused by a non-alpha variant and one viral strain could not be identified. The vaccine efficacy was 89.7% (95% CI: 80.2-94.6).

- Vaccine efficacy was 88.9% (95% CI: 12.8-98.6) in participants 65 years of age or older. A total of 10 COVID-19 cases were reported in this age group; one in the vaccine group and nine in the placebo group.

- There were no hospitalizations or deaths from COVID-19 among the vaccine group. Of the 96 individuals in the placebo group with COVID-19 infection, there were 5 cases of severe infection; one patient was hospitalized, three went to an emergency department and one received care at home. Disease severity was determined based on a pre-defined algorithm.[1]

Intention-to-treat Population (N=15,139)

- The intention-to-treat (ITT) population included participants that received at least one dose of vaccine (n=7,569) or placebo (n=7,570). The vaccine efficacy was 70.4% (95% CI: 58.3-79.1) for the ITT population.

- There were 2 deaths related to COVID-19 in the ITT population. One was in a vaccine recipient that developed symptoms 7 days after the first dose, was hospitalized for respiratory failure and died 15 days after vaccine administration. The other individual was in the placebo group who was hospitalized 24 days after dose one and died 4 weeks after hospitalization from complications of COVID-19 pneumonia and sepsis.

Adverse Events:

- The ITT population (N=15,139) was assessed for unsolicited adverse events from the first dose to 28 days after the second dose. There were no occurrences of anaphylaxis. Adverse events occurred more often in the vaccinated group compared to placebo (25.3% vs. 20.5%). However, the incidence of severe (1.0 vs 0.8%), serious (0.5 vs. 0.5%), medically attended (3.8 vs. 3.9%) and adverse events leading to discontinuation of dosing (0.3 vs. 0.3%) or participation in the trial (0.2 vs. 0.2%) was similar between groups. One vaccine recipient experienced myocarditis three days after the second dose but recovered after 2 days of hospitalization. It was determined by an independent safety monitoring committee that this event was likely a viral myocarditis.

- Adverse events were solicited in a subgroup of 2,310 participants using an electronic diary for 7 days after each dose. Local and systemic adverse events were reported more frequently in the vaccine group than in the placebo group after the first and the second dose. Most of the adverse events were mild to moderate, of short duration and more common after the second dose. The most common local adverse events amongst vaccine recipients were injection

tenderness or pain and were reported more frequently among younger vaccine recipients (18 to 64 years of age) than among older recipients (≥65 years). The most common systemic adverse effects were headache, muscle pain and fatigue. The incidence of serious adverse events was similar between groups (0.5 vs. 0.5%) and no deaths were attributed to the vaccine.

PHO reviewer's comments

- In this clinical trial of Novavax, the overall vaccine efficacy for preventing symptomatic disease was 89% which is comparable to that seen with mRNA vaccines but higher than that seen with viral vector vaccines. In phase 3 studies of other COVID-19 vaccines approved for use in Canada, vaccine efficacy for prevention of symptomatic disease was 94-95% for mRNA vaccines (Moderna COVID-19 vaccine [mRNA-1273], Pfizer-BioNTech COVID-19 [BNT162b2] and 67-70% for viral vector vaccines (Janssen/Johnson & Johnson [JNJ78436735/Ad26.COV2.S], Oxford University/AstraZeneca [AZD1222/ChAdOx1-S]).[2–5]

Strengths

- This is an observer-blinded, placebo-controlled trial of adults who were randomized in a 1:1 ratio to receive two intramuscular 5-µg doses of NVX-CoV2373 or placebo. Approximately 45% of the participants had at least one coexisting comorbidity which included chronic respiratory, cardiac, renal, neurologic, hepatic, and immunocompromising conditions as well as obesity, which contrasts with clinical efficacy trials of other COVID-19 vaccines.

- The Novavax vaccine is stored at standard refrigerator temperatures (2-8 ^{o}C) and does not need ultra-cold storage or thawing before use. This is advantageous over mRNA vaccines which have these stringent storage and handling requirements, especially in the context of widespread administration in various settings.

Limitations

- This study does not provide any data on vaccine efficacy for asymptomatic infection or transmission; however, vaccine efficacy for prevention of hospitalizations or severe disease was 100%. As vaccine efficacy was based on a relatively short time frame of observation (median 3 months after dose 2), ongoing follow-up data will provide additional information on vaccine efficacy.

- This study provides very limited data on vaccine efficacy in special populations or subgroups. For example, while the trial demonstrated vaccine efficacy of 88.9% for prevention of symptomatic infection in older adults 65 years or greater and similar efficacy in participants with and without coexisting medical conditions, individuals with immunodeficient conditions were excluded.

- A further limitation of the current trial is the lack of sequencing data on viral isolates, although the use of S-gene target failure, as detected by the TaqPath assay, has proved to be a reliable proxy for the presence of B.1.1.7 variants. Further data is needed to evaluate Novavax vaccine efficacy and effectiveness against other variants of concern (e.g., delta).

- While the initial safety profile appears acceptable, the incidence of rare adverse events cannot be assessed based on the number of participants in this study and the relatively short observation period following vaccination. An ongoing study will evaluate serious adverse

events, adverse events of special interest and medically attended adverse events from the first dose through 1 year after the second dose.

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Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of "Safety and efficacy of NVX-CoV2373 covid-19 vaccine". Toronto, ON: Queen's Printer for Ontario; 2021.

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