

SYNOPSIS

Review of “Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico”

10/13/2021

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One-minute summary

- This is a phase 3, randomized, observer-blinded, placebo-controlled trial evaluating the efficacy and safety of **NVX-CoV2373 (Novavax), an adjuvanted protein subunit vaccine**, in preventing symptomatic mild, moderate or severe COVID-19 in SARS-CoV-2-naïve adults at least 7 days after receiving the second vaccine injection.
- Of the 29,949 individuals randomized between December 27, 2020, and February 18, 2021, 29,582 participants received at least one dose of NVX-CoV2373 (n=19,714) or placebo (n=9,868); 25,452 (n= 17,312 for NVX-CoV2373, n= 8,140 for placebo) met criteria for inclusion in the per protocol population of efficacy (PP-EFF).
- The primary end point of vaccine efficacy (VE) in preventing the first episode of reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed COVID-19 with onset ≥ 7 days after the second injection in the PP-EFF cohort was 90% (95% Confidence Interval [CI]: 83-95).
 - This was based on a total of 77 COVID-19 cases; 63 in the placebo (34 cases per 1000 person years, 95% CI: 21-56) and 14 in the NVX-CoV2373 group (3.3 cases per 1000 person years, 95% CI: 1.6-6.9). Cumulative incidence of COVID-19 in the vaccine group was highest in the first 42 days of follow up, after which incidence declined while continuing to increase in the placebo group.
 - The VE was 100% (95% CI: 87-100) against moderate-to-severe COVID-19 and 100% against severe COVID-19 (95% CI: 35-100). All COVID-19 cases in the NVX-CoV2373 group were mild whereas there were 14 moderate-to-severe cases in the placebo group.
 - The VE against non-variants of concern/variants of interest (VOC/VOI) was 100% (95% CI: 86 -100); VE against any VOC/VOI was 92.6% (95% CI: 84 to 97). Most VOC (89%) were identified as variant Alpha; VE against Alpha was 94% (95% CI, 82 to 98).

- Solicited local and systemic adverse events (AEs) occurred more frequently in NVX-CoV2373 recipients and after the second injection. These were mostly mild-moderate in severity and transient; tenderness and injection site pain were most commonly reported; for example tenderness was reported in about 50% of NVX-CoV2373 group after the first dose and more than 60% after the second dose compared with less than 20% in placebo group after the first or second dose with a median duration ≤ 2 days. Severe local reactions were infrequent, but occurred more frequently in the NVX-CoV2373 group and after the second dose (6.7% vs. <1% after dose 2 in the NVX-CoV2373 and placebo groups, respectively). For vaccine recipients, systemic AEs occurred more frequently after the second dose and were transient (median duration of ≤ 1 day). The most common systemic AEs in this group were headache, myalgia, fatigue and malaise; the incidence of these AEs was higher after the second dose (approximately 15-30% after the first dose compared with about 35-40% after second dose).
- Unsolicited AEs were slightly more frequent in vaccine than in placebo recipients (16.3% vs. 14.8%), although there was a balanced frequency of medically-attended adverse events (MAAEs), serious AEs (SAEs), adverse events of special interest (AESIs) related to COVID-19. There were no episodes of anaphylaxis or Guillain Barré syndrome (GBS). No imbalance in myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome (TTS) or all-cause mortality was observed between groups.

Additional information

- **Study Participants:** individuals were enrolled from 113 sites across the US and 6 sites in Mexico enrolled; those ≥ 18 years of age including those with stable chronic medical conditions (e.g. chronic pulmonary, renal, or cardiovascular disease, diabetes mellitus type 2, or well-controlled human immunodeficiency virus (HIV) infection). Individuals with known previous laboratory documented SARS-CoV-2 infection or known immunosuppression were excluded. Participants were stratified by age (18 to ≤ 64 or ≥ 65 years) and randomized in a 2:1 ratio to receive two 0.5 mL intramuscular injections of either NVX-CoV2373 (5 μ g full-length, stabilized pre-fusion, recombinant S (rS) SARS-CoV-2 vaccine adjuvanted with 50 μ g Matrix-M™) or placebo 21 days apart. Participants received initial injections between December 27, 2020, and February 18, 2021, and were followed through April 19, 2021.
- **Data Collection:** Symptoms of suspected COVID-19 were assessed daily by participants using an electronic diary. Participants performed self-collection of three daily nasal swabs and underwent in-clinic medical evaluation and provider-collected nasal swab collection for SARS-CoV-2 testing using reverse transcriptase polymerase chain reaction (RT-PCR) testing if symptoms were reported for more than two consecutive days. Safety was assessed by evaluating solicited local and systemic adverse events collected by electronic diary and by assessing participants for unsolicited adverse events (AE) including serious adverse events (SAE), adverse events of special interest (AESIs) and medically attended adverse events (MAAE) from the first dose with a median follow-up of two months. Long-term safety monitoring is planned to continue throughout the 24 months after initial vaccination.
- **Analysis:** The PP-EFF used for all efficacy analyses included participants without evidence of past SARS-CoV-2 infection at baseline until ≥ 7 days after the second injection and had received both injections of assigned treatment. Vaccine efficacy (VE%) was defined as $(1 - RR) \times 100$, where RR is the relative risk of infection rates between the two groups. Due to Emergency Use

Authorization (EUA) approval of other COVID-19 vaccines and national rollout of COVID-19 vaccines, a blinded crossover design was implemented after achieving FDA-required 2 month placebo-controlled safety follow-up to enable all participants to receive an active COVID-19 vaccine as soon as possible.

- **Patient Characteristics:** baseline demographics of the PP-EFF were balanced between treatment groups; 48.2% self-identified as female and the median age was 47 years. One or more comorbid conditions were reported by 47.3% and 11.8% were ≥ 65 years of age. With respect to race or ethnicity, 75.9% self-identified as white, 21.5% as Hispanic/Latino, 11.0% as Black/African American and 6.2% as Native American/Alaska Native.
- **Variants of Concern:** Whole-genome sequencing (WGS) was performed on 61 out of 77 (79%) nasal swabs, which resulted in identification of 35 VOC, 13 VOI, and 13 non-VOC/VOI. Most VOC (89%, n=31) were identified as variant Alpha; the others were identified as variant Beta (n=2) and variant Gamma (n=2).

PHO reviewer's comments

- This study is currently published as a pre-print and is yet to undergo peer-review. As such, the authors' findings still require formal assessment prior to publication in a peer-reviewed journal.
- This study demonstrates that NVX-CoV2373, which is an adjuvanted protein subunit vaccine, is highly effective against preventing symptomatic and severe COVID-19 in SARS-CoV-2 naïve individuals with an acceptable safety profile. The overall VE of 90% (7 or more days after 2 doses of vaccine) is comparable to VE reported in phase 3 trials of the mRNA vaccines (Pfizer-BioNTech Comirnaty® BNT162b2, Moderna Spikevax® mRNA-1273),¹⁻³ and somewhat higher than that reported in phase 3 trials of the viral vector vaccines (AstraZeneca Vaxzevria™ AZD1222 and Johnson & Johnson Ad26.COVS.2.S).^{4,5}
- Trial enrollment incorporated ethnic and racial diversity as well as a high proportion of participants reporting one or more comorbid conditions with the vast majority of participants being less than 65 years of age. While VE was generally similar across demographic subgroups, an important limitation is that low enrollment of individuals ≥ 65 did not allow for a meaningful assessment of VE in this group. However, a Phase 3 trial of NVX-CoV2373 in the UK found that the VE for adults ≥ 65 (88.9%, 95% CI: 79.7-95.5) to be comparable to the adults 18 to < 65 years (89.8%, 95% CI: 79.7-95.5).⁶
- This study provides minimal data on the impact of vaccines on VOC other than alpha, due to the early time period in which the study took place. More recent data will be necessary to determine VE for other current circulating VOC.
- NVX-CoV2373 is stored at refrigerator temperature (2-8 degrees C) for up to 6 months which is an advantage for widespread global deployment. As NVX-CoV2373 uses a conventional vaccine platform, use of this vaccine may also be beneficial in helping to overcome vaccine hesitancy related to new mRNA technology and extend the durability of protection. NVX-CoV2373 is not authorized for use in Canada at this time and is currently under review by Health Canada and World Health Organization (WHO) emergency use listing.⁷

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Citation

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