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SYNOPSIS

Review of "Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age"

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One-minute summary

- This article describes the evaluation of the BNT162b2 Coronavirus Disease 2019 (COVID-19) vaccine in children 5 to 11 years old which is based on a phase 1, dose-finding study and an ongoing phase 2/3 randomized controlled trial to determine the safety, immunogenicity (Pediatric Study C4591007) and efficacy of two doses of the BNT162b2 vaccine administered 21 days apart. Over 2,000 children aged 5 to 11 years across the United States and Europe were included in this study.

- Immune responses, as measured by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibody titres 1 month after the second dose, in children 5 to 11 years of age were found to be non-inferior when compared with young adults 16-25 years of age (from Phase 1/2/3 Registrational Study C4591001). A descriptive analysis found vaccine efficacy (VE) to be 90.7% (95% Confidence Interval [CI]: 67.7 to 98.3%) against symptomatic COVID-19 at least 7 days after the second dose in those without prior infection. There were no cases of severe disease (elevated respiratory rate/heart rate, shock, end organ dysfunction, or Intensive Care Unit admission).

- Side effects from the vaccine were generally mild to moderate, occurring within two days of vaccination and were transient, resolving within one to two days. Commonly reported mild to moderate side effects included local injection site pain, redness and swelling, and systemic effects of fatigue, headache, muscle and/or joint pain, chills, fever, swollen lymph nodes, nausea and decreased appetite. More children reported side effects after the second dose than after the first dose. No serious adverse events following the vaccine were reported in the clinical trial, including no events of anaphylaxis, myocarditis or pericarditis.

- The U.S. Food and Drug Administration authorized the emergency use of the Pfizer-BioNTech Comirnaty COVID-19 vaccine for 5-11 year olds on October 29, 2021. Health Canada is currently reviewing the manufacturer's submission and authorization is imminently expected – this study demonstrates administration of two 10 mcg doses of BNT162b2 21 days apart to children 5 to 11 years of age was safe, immunogenic, and efficacious.

Additional information

- **Study Participants**: In the **Phase 1, Open Label, Dose-Finding Study**, doses of 10, 20 and 30 mcg were assessed in 48 children 5 to 11 years old (16 children at each dose level). Children with a previous clinical or lab-confirmed COVID-19 infection were excluded. The 10 mcg dose was found to have a more acceptable safety profile and comparable immunogenicity to the 20 mcg dose. In the **Phase 2-3 Study,** the initial enrollment group included 2,268 participants randomized 2:1 to vaccine (n=1,518) or placebo (n=750). Children with stable or no pre-existing conditions were eligible; those with an immunocompromising or immunodeficiency disorder, history of Multisystem Inflammatory Syndrome - Children (MIS-C), or receiving immunosuppressive therapy were excluded. Median age was 8.2 years; baseline SARS-CoV-2 status was 8.8% in the vaccine group and 8.7% in the placebo group (in the Phase 2-3 study, patients with prior SARS-CoV-2 infection were not excluded). The initial enrollment group had a median follow-up of 2.3 months.

- **Phase 2-3 Immunogenicity:** Immunogenicity was assessed by calculating the ratio of geometric mean titres (GMTs) and the difference between the percentage of patients with a seroresponse (comparing 5-11 year olds and 16-25 year olds). Serum samples of the two age groups were assayed in parallel to improve comparability between titres. SARS-CoV-2 50% neutralizing titres elicited by a two-dose primary series of BNT162b2 (10 mcg) in children 5 to 11 years old were determined to be non-inferior to those elicited in young adults 16 to 25 years old by a two-dose primary series of BNT162b2 (30 mcg). This was based on immunobridging analyses using a validated SARS-CoV-2 neutralization assay in 485 children from the initial enrollment group (322 vaccine recipients, 163 placebo), compared with a random sample of 350 young adults aged 16 to 25 years old from Registrational Study C4591001 (300 vaccine recipients, 50 placebo).

- **Phase 2-3 Vaccine Efficacy (VE):** Vaccine efficacy against symptomatic COVID-19 7 or more days after the second dose in those without evidence prior infection was 90.7% (95% CI: 67.7 to 98.3%), where VE was defined as 100 × (1 – Incidence rate ratio [IRR]) and IRR is the rate ratio of confirmed COVID-19 illness in the vaccine group (3 cases) to that in the placebo group (16 cases). Among all patients regardless of prior infection, VE was 90.7% (95% CI, 67.4 to 98.3%). No cases of severe disease were reported. All cases were lab-confirmed and reported when Delta was the predominant circulating strain from July – October 8, 2021.

- **Phase 2-3 Safety:** Reactogenicity events were reported by a parent or guardian using an electronic diary for 7 days after each dose. Data on unsolicited adverse events were collected from the first dose through 1 month after the second dose. Data on serious adverse events will be collected from the first dose through 6 months after the second dose. Adverse events were generally mild-moderate and lasted 1-2 days, with injection site pain being the most common local reaction, which occurred in 71-74% of vaccine recipients. In this study, children 5 to 11 years old reported more local reactions than adolescents 12-25 years of age in a previous study (redness [15-19% vs. 5-7%], swelling [10-15% vs. 5-8%); however, the rate of systemic events such as fever and chills were lower in the pediatric study (fever [3-7% vs. 1-20%], chills [5-10% vs 6-42%]).[1]

PHO reviewer's comments

- While a primary VE analysis could not be performed due to the low number of events, the descriptive analysis indicated a high VE of 90.7% consistent with a VE of 95% from the pivotal trial which included young adults aged 16 to 25 years old.[2]

- This study provides supporting evidence for the efficacy of BNT162b2 against COVID-19 in children, including infections caused by the Delta variant. During the time frame and locations of this study, Delta was the predominant circulating variant. In an FDA briefing document, the manufacturer indicates that a two-dose primary series of BNT162b2, 10 mcg given to children 5 to 11 years of age appears to be effective against the Delta variant. Serum neutralizing titres against the Delta variant were comparable to those against wild-type strain in a small sample of 38 randomly selected participants aged 5 to 11 years 1 month after the second dose.[3]

- While there were no reports of serious adverse events such as anaphylaxis, myocarditis, pericarditis, Bell's palsy, appendicitis, MIS-C, Kawasaki disease, thrombocytopenia, venous thromboembolism or meningitis, this study was underpowered to detect rare events. Additionally a longer follow-up time will be important in monitoring for serious adverse events. While the median follow-up was 2.3 months in the initial enrollment group in this study, the duration of follow-up in the additional safety expansion group was very short at 2.4 weeks (Ref: VRBPAC Briefing Document). The study plans to follow participants for 2 years after receipt of the first dose.

- To improve vaccine stability, the pediatric formulation contains a Tris buffer which is used in other vaccine products such as Moderna vaccine. Also known as tromethamine or trometamol, Tris buffer has been associated with allergic reactions in other compounds such as contrast media, oral and parenteral medications.[4]

- Other limitations of the study included:

    - The follow-up to assess the duration of immune responses, efficacy, and safety was relatively short.

    - Only humoral and not cell-mediated immune response results were presented.

    - Concomitant administration of BNT162b2 with other vaccines was not assessed.

References

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Citation

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