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Discrepancies of Pediatric Data of BNT162b2 mRNA Covid-19 Vaccine in the Assessment Report of the European Medicines Agency

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ABSTRACT

Severe cases of Covid-19 predominantly occur in the elderly and subjects with underlying conditions. However, it is a mild disease in most of the affected people, particularly children and adolescents. This paper comments on the Assessment Report of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) (herein further referred to as Assessment Report) on the data of pediatric study; the Assessment Report served as a basis for authorization of Comirnaty vaccine for active immunization to prevent Covid-19 in individuals 12 to 15 years of age. By the legislation of the European Union, Assessment Report is a key document for an opinion of EMA regarding marketing authorization. Opinion of EMA provides a background for a decision of the European Commission to place a medicinal product for human use on the market.

Abbreviations: EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use; SAEs: Serious Adverse Events

Clinical Efficacy

The Assessment Report of pediatric study of BNT162b2 mRNA Covid-19 Vaccine (Comirnaty) says that there was no cases of Covid-19 in 1119 adolescents 12 to 15 years of age administered vaccine (0%) and there were 18 cases in 1110 (1.6%) of those administered placebo [1]. The vaccine efficacy (Relative Risk Reduction, ARR) is 100% while the Absolute Risk Reduction (ARR) is 1.6 % (18/1119 – 0/1110) [1]. Literally, BNT162b2 mRNA Covid-19 Vaccine prevented mild Covid-19 in 1.6% of the study population. At the cut-off date, no severe cases and no deaths were reported in 12 15 years-old age group1, i.e., no benefit in respect to prevention of severe or death Covid-19 was demonstrated. Prevention of long-term Covid-19 was not investigated.

Safety: Serious Adverse Events

The Assessment Report says that the rate of Serious Adverse Events (SAEs) in adolescents in the time frame from dose 1 to one

month after dose 2 (until the data cut-off, 13 March 2021) was very low and similar between vaccine and placebo arms (≤0.4%).1 However, it is a misleading statement:

1) Mixing an active drug arm and a control arm is unacceptable from a scientific point of view. Indeed, there were 5 serious adverse events (SAEs) in the vaccine arm and 2 SAEs in the placebo arm; serious psychiatric events were reported in 4 subjects in the vaccine arm and 0 in the placebo arm [1].

2) In addition, 2 adolescents originally randomized to the placebo had life-threatening SAEs after they turned 16 years during the study and were unblinded to receive BNT162b2, [1]

3) Frequency category "very low" is not consistent with the Medical Dictionary for Regulatory Activities (MedDRA). According to MedDRA, the SAEs should be classified as uncommon (frequency ≥1/1,000 to <1/100).

5 above-mentioned SAEs in adolescents of the BNT162b2 group included [1]:

1) Participant No 1 had neuralgia with 3 emergency room visits beginning day 1 after dose 2 and subsequently, abdominal pain and constipation. She was diagnosed with functional abdominal pain, referred to psychology and physical therapy after which symptoms were reported as gradually improving. However, SAEs persisted after 1-month post Dose 2 and remained unresolved at the data cut-off (see follow up below),

2) Participants No 2 and 3 had depression,

3) Participant No 4 had concurrent anxiety and depression,

4) Participant No 5 had concurrent appendicitis and focal peritonitis.

2 adolescents originally randomized to the placebo group had life-threatening SAEs after they turned 16 years of age and were unblinded to receive BNT162b2 [1]:

1) Participant No 6: an anaphylactoid reaction reported 3 days after receiving the first dose of BNT162b2 with a duration of 1 day, leading to study withdrawal,

2) Participant No 7: a depression reported 7 days after receiving the first dose of BNT162b2 reported as ongoing/resolved at the time of data cut-off date.

SAEs reported from after 1-month post Dose 2 up to the data cut-off date included suicidal ideation and appendicitis (each appearing in 1 participant) [1]. In participants administered placebo 2 SAEs have been reported [1]. Follow-up data, consistent with Participant No 1, was presented on 28 June 2021 during a meeting organized by Senior United States Senator from Wisconsin Ronald Harold Johnson. Stephanie de Garay described the experiences of her daughter Maddie de Garay after the 2nd dose of the Pfizer Covid-19 vaccine in the pediatric study. Upon receiving her second dose on January 20th, over the next 24 hours, Maddie developed severe abdominal and chest pain. She had extreme pain in her fingers and toes making them turn white and cold. Later, abdominal, muscle, and nerve pain became unbearable. Additional symptoms included gastroparesis, nausea and vomiting, erratic blood pressure and heart rate, memory loss. She mixed up words, had brain fog, headaches, dizziness, fainting, and then seizures, developed verbal and motor tics. She lost feeling from the waist down and got muscle weakness, drastic changes in her vision, urinary retention and loss of bladder control, severe irregular menstrual cycles, and eventually got a nasogastric tube for her nutrition [2].

Discussion

By article 14-a (1) of the Regulation (EC) 726/2004, conditional marketing authorization for medicinal products intended for the treatment or prevention of seriously debilitating or life-threatening diseases may be granted before the submission of comprehensive clinical data [3]. However, Covid-19 is neither a debilitating nor life-threatening disease in the majority of adolescents [4]. Severe cases occur rarely, and predominantly in subjects with underlying conditions, adolescents with risk of severe disease due to underlying conditions were not specifically studied [1]. The study did not demonstrate any benefit in respect to the prevention of severe Covid-19. It demonstrated more SAEs instead: 5 adolescents in the BNT162b2 group reported any SAE from Dose 1 to the data cut-off date up to 1 month after Dose 2. Two adolescents originally randomized to the placebo group had life-threatening SAEs after they turned 16 years during the study and were unblinded to receive BNT162b2. These SAEs are not included in the benefit-risk assessment of the Assessment Report [1]. By the report of the Centers for Disease Control and Prevention from 1 March 2020 to 24 April 2021, the cumulative Covid-19–associated adolescent hospitalization rate was 49.9 per 100,000.2 If we assume that vaccines prevent all cases of severe Covid-19 (49.9/100,000), the absolute risk reduction is 0.05%, i.e., 2000 vaccinations might prevent 1 hospitalization. This means that effectiveness in respect to the risk of hospitalization was about 10 times lower than the frequency of SAEs (by definition, SAE results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or a congenital anomaly/birth defect) [4].

COVID-19 pandemics did not increase pediatric mortality in EUROMOMO countries. Instead, pediatric mortality steadily decreased from spring 2020 until June 2021, i.e., beginning of the pediatric vaccination against COVID-19 [5]. Time relation does not mean causation but still should be considered. The pediatric study did not provide data to what extent vaccination provides protection

against asymptomatic infection, and whether vaccination prevents further transmission.1 The pediatric data came from the period before the emergence of the Delta variant. There are no bridging studies to extrapolate the pediatric data to today's situation. The power of the pediatric study was neither sufficient to demonstrate any benefit in terms of reduction of the risk of severe COVID-19 or death nor the risk of serious or life-threatening adverse reactions. It should also be noted that the BNT162b2 mRNA Covid-19 vaccine has been used for mass vaccination in children and therefore any doubt regarding safety or efficacy is unacceptable [6,7].

Conclusion

1) Covid-19 should not be considered a serious, debilitating, or life-threatening disease in 12 to 15-years-old adolescents, i.e., conditions of the conditional marketing authorization are not met.

2) Known benefits of the BNT162b2 vaccine in 12 to 15-years-old adolescents do not exceed known risks. In addition, long-term risks are unknown.

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