EMA/134030/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005735/II/0111

Invented name: COMIRNATY

International non-proprietary name: tozinameran

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Timetable	Date
Start of procedure	07 Feb 2022
CHMP Rapporteur Assessment Report	16 Feb 2022
CHMP members comments	18 Feb 2022
ETF meeting	18 Feb 2022
Updated CHMP Rapporteur Assessment Report	18 Feb 2022
PDCO consultation	22 Feb 2022
Opinion	24 Feb 2022

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 04 February 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.2 of the SmPC of Comirnaty 30 microgram/dose to lower the age of the booster dose from adults 18 years of age and older to adults and adolescents 12 years of age and older, based on real world evidence collected by the Ministry of Health of Israel. The Package Leaflet is updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes throughout the product information (SmPC and package leaflet).

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Introduction

The indication for COMIRNATY (30 µg) is:

-Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

The homologous booster dose of BNT162b2 (30 µg), administered at approximately 6 months after Dose 2 for individuals ≥18 years of age was approved on 05 October 2021 in the EU. This decision was based on the data on immunogenicity and safety for a group (N= 268) of Phase 3 participants, who received a booster dose in Phase 1/2/3 Study C4591001, which is the registrational and pivotal study.

EMA is evaluating in parallel vaccine efficacy and safety of the 3rd dose of Comirnaty (30 µg) for individuals ≥18 years of age and a potential extension of the booster recommendation to individuals from 16 years of age under the EMEA/H/C/005735/II/0093 procedure, which is based on study C4591031. This is a continuation study of the pivotal C4591001 study. Study C4591031 is the ongoing, randomized, placebo-controlled, Phase 3 booster efficacy study, where approximately 10,000 individuals ≥16 years of age randomized 1:1 to receive a booster dose of BNT162b2 30 µg or placebo at least 6 months after completing the 2-dose primary series in Study C4591001 and followed up to at least 2 months post-booster.

EMA requested the MAH to submit the data on booster use in adolescents (12-15 years old) for assessment:

a) EMA would be interested to understand, within this submission, what data are additionally generated by you (or by 3rd parties) and the timelines of their availability.

b) In addition, there is a particular interest in understanding the safety of such booster administration (particularly from Real World Evidence, i.e., not limited to clinical trial data), and here particularly any information/data you have as regards cases of myocarditis following such a booster dose.

To address this request, the MAH has assembled the most current information available in Clinical Overview and submitted it along with 3 publications (Barda et al; Bar-on et al and Arbel et al.) describing

Real World Efficacy of third dose in Israel among adults over 37 years of age and slide-set describing safety of the third and fourth dose of Comirnaty (30 microg) in Israel.

Background for Lowering the Age for the Booster Dose to Individuals 12 Years of Age

On 03 January 2022, the US FDA extended the Emergency Use Authorization for Pfizer BioNTech COVID-19 Vaccine to allow administration of a single booster dose to individuals 12 through 15 years of age who have completed a primary series with Pfizer-BioNTech COVID-19 vaccine based upon their review of data not generated by Pfizer or BioNTech.

The reduction in the age of the booster dose to 12 years is based on the following:

-Safety data from the Israel Ministry of Health showing that after administering a single booster dose to more than 6,000 12- to 15-year-olds, no new safety concerns were identified through 15 December 2021[i]

-Data showing that a single booster dose can greatly improve effectiveness against a range of SARS-CoV-2 outcomes compared to after only two doses administered at least five months ago and

-Emerging evidence suggesting that three doses of vaccine may be especially necessary for preventing omicron related disease.

Post-Marketing Safety Data

Summary of Post-Marketing Safety Data Reported to Pfizer/BioNTech

Post-authorization adverse event reports are monitored for safety information reported in association with a third dose (in immunocompromised individuals) and booster dose of COVID-19 mRNA Vaccine (nucleoside-modified) (COMIRNATY®), and have been described in summary safety reports, since the approval of the use of a third/booster dose. The AE reports received following a third/booster dose of COMIRNATY have been consistent with the known safety profile of the vaccine observed in the primary dosing series. No new safety concerns have arisen specifically from third/booster dose information.

Clinical Trial Data

Study C4591031

Study C4591031 is a Phase 3 master study designed to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Substudy B and Substudy C, described below, include evaluation of booster dosing in individuals ≥12 years of age.

Substudy B

Substudy B is a randomized, placebo-controlled, observer-blind, crossover substudy to evaluate the safety and tolerability of a booster (third) dose of BNT162b2. Participants ≥12 years of age to ≤30 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 6 months (≥8 months for those 12-17 years of age) prior to randomization will be enrolled. Participants will be randomized at a ratio of 1:1 to receive either BNT162b2 or placebo at Visit 1 and the alternative at Visit 3, four weeks later. Randomization will be stratified by age (stratified as 12-17, 18-24, and 25-30 years of age). Approximately 1500 participants will be randomized in the study. A blood sample will be collected to obtain a serum sample for troponin testing before each administration of blinded study intervention, 2 to 5 days after each administration, and 1 month after the second administration.

Substudy C

Substudy C is a randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of a booster (third) dose of BNT162b2 at 10 µg and at 30 µg. Participants ≥12 years of age who have completed a 2-dose primary series of BNT162b2 (30-µg doses) at least 6 months (≥8 months for those 12-17 years of age) prior to randomization will be enrolled. Participants will be

randomized at a ratio of 1:1 to receive BNT162b2 at either a 10-µg or 30-µg dose level at Visit 301. Randomization will be stratified by age with escalation to each higher age group guided by immunogenicity results at 7 days after the third dose. A DMC will review safety (e-diary and AE) and immunogenicity data in the first approximately 100 participants with available immunogenicity data in each age group (~50 participants in each dose level) 7 days after the third dose. Upon confirmation of an acceptable safety and immunogenicity assessment by the DMC, progression of the next age group will occur independently.

Timelines for Availability of Clinical Trial Data Relevant to Booster Dosing in Individuals ≥12 Years of Age

The MAH has targeted Q2 2022 for the availability of data from Study C4591031 substudies that will evaluate the booster dose in individuals ≥12 years of age. However, following approval in the United States of a booster dose from the age of 12 years under Emergency Use Authorization (EUA) and subsequent availability of a booster dose for this age group outside of clinical trial setting, there may be challenges in achieving this timeline.

Post-Authorization Safety Studies (PASS)

Pfizer is conducting five (5) post-authorisation safety studies (PASS) that will include data on booster doses among individuals 12 to 15 years of age. Three studies use large electronic healthcare databases to assess increased risk of safety events of interest: C4591009 and C4591011 in the United States (US) and C4591021 in Europe. Two additional studies focus on individuals with myocarditis/pericarditis following vaccination with COMIRNATY, including the booster dose: C4591036, a low-interventional primary data collection study in the US and Canada and C4591038, a substudy of C4591021 in Europe. To date, C4591009, C4591011, C4591036, and C4591038 are still in planned status. While C4591021 is ongoing, there are no safety data available for children 12-15 years of age who have been vaccinated with a booster dose at this time; an upcoming interim report is planned for 31 March 2022.

3. Clinical Efficacy aspects

The RWE publications submitted by MAH during this variation are summarized below:

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel (Bar-on et al)

Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study (Barda et al)

BNT162b2 Vaccine Booster and Mortality Due to Covid-19 (Arbel et al.)

3.1. Discussion

Comirnaty was shown to elicit non-inferior immune responses in subjects 12-15 years of age without previous COVID-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2 (study C4591001, variation EMEA/H/C/005735/II/0030).

Specifically, responses in adolescents were superior to the older age group, reflecting by greater geometric mean-fold rise (GMFR) of SARS-CoV-2 50% serum neutralizing titers in the 12-15 years group (GMFR 118.3 (CI95% 101.4, 137.9)) compared to 16-25 age group (GMFR 71.2 (CI95% 61.3, 82.7) at 1 month after dose 2).

A high proportion of participants (97.9% of adolescents and 100.0% of young adults) had a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month post-dose 2.

The ability to boost the vaccine-induced immune response was established in study C4591001, variation EMEA/H/C/005735/II/0067. Here, it was shown that a booster dose results in antibody titres that are considerably higher than those observed after the 2nd dose. The SARS-CoV-2 neutralizing GMT ratio of 1 month after Dose 3 to 1 month after Dose 2 was 3.29 (2-sided 97.5% CI: 2.76, 3.91), which met the 1.5-fold noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI for GMR >0.67) and point estimate of GMR ≥0.8.

For more details please refer to variation EMEA/H/C/005735/II/0030 and EMEA/H/C/005735/II/0067.

The booster effects were mainly studied in adults 18 to 55 years of age. In this population, it has been shown that a third dose given approximately 6 months after the primary vaccination series more than restores neutralising titres, compared to what was seen one month after dose two. While the immunogenicity and reactogenicity of a third dose have been sufficiently characterised, the proper timing and impact of a third dose across different populations has not been established. The antibody titres in adolescents are generally higher than those observed in adults, which may lead to longer protection after the primary series in adolescents as compared to adults, albeit there are no data to underpin this.

The three publications from Israel are based on registry data. Israel started to vaccinate their adult population with Comirnaty 30 µg earlier than rest of the world, therefore it was also noticed there that immunogenicity waned gradually after the second dose. In the summer of 2021, the Delta variant appeared in Israel. At this time, also double vaccinated people started to present with symptomatic infections. Therefore, the Israeli Ministry of Health and the government decided to offer the third dose of Comirnaty 30 µg first for elderly and after to all adults. Current publications describe the efficacy of 3 doses of Comirnaty compared to 2 doses. During the summer months around 800 000 individuals who had at least 5 months passed from their second dose, received their booster dose.

Health registries provided the opportunity to compare incidence of infection, illness, and death due to COVID-19 in age matched adult cohort who had received either 2 or 3 doses of Comirnaty. The big improvement of vaccine efficacy 3 doses compared to 2 doses against mainly Delta variant was noticed in adults from 37 years of age. Unfortunately, no data for younger people has been published from Israel as at the time of the study, young people had not yet received a third dose.

These publications strengthen the evidence of efficacy of the booster dose, which is also demonstrated in the MAH clinical trial including smaller cohort (n= 10,000) from age 16 and older (study C4591031, assessed in the EMEA/H/C/005735/II/0093 procedure).

In conclusion, Comirnaty has been shown to be at least as good at inducing neutralising antibody titers after the primary series in adolescents as in adults, and while the ability to boost the vaccine-induced immune response was only shown in adults, a booster response to the vaccine can be equally expected in adolescents.

4. Clinical Safety aspects

The main safety data included in this submission are derived from a summary of spontaneously reported events following vaccination in Israel.

4.1. Discussion

The unfavourable effects of vaccination with Comirnaty have been well characterised in clinical trials. The unfavourable effects are mainly AEs associated with reactogenicity that are limited in severity and duration and are fully reversible. Observational data derived from the vaccination campaigns in different

countries have generally confirmed this safety profile. Unfavourable effects that have been detected upon the wide-spread use are myo/pericarditis, erythema multiforme and swelling of the vaccinated limb.

In general the unfavourable effects of the primary series administered to adolescents 12-15 years of age was considered to be similar to that seen in participants 16 years and older. The unfavourable effects of a booster administration have been evaluated in the same trial as the immunogenicity of a booster dose (study C4591001, variation EMEA/H/C/005735/II/0067). In individuals 18-55 years of age the safety of a booster dose was regarded as comparable to that of the primary series.

Given that the unfavourable effects of the primary series are comparable in adolescents and adults (reactogenicity was slightly higher among adolescents, while adverse events were similar or lower) and given that the unfavourable effects of the booster dose in adults are comparable to that of the primary series, there is no indication that the unfavourable effects of the booster dose in adolescents would be substantially different than the unfavourable effects of the primary series in adolescents.

As regards the characterisation of rare and very rare potentially serious unfavourable effects some observational data are available.

Myocarditis and pericarditis have been observed in younger men more often following the second vaccination of the primary series. From observational data no increase in reporting rate has been described following the booster injection.

The submitted safety information from the Israeli Ministry of Health shows that after administering a single booster dose to more than 6,000 12- to 15-year-olds, no new safety concerns were identified through 15 December 2021.

Further data will be submitted for assessment in the remit of the PSURs and summary safety reports as well as the substudies B and C from study C4591031.

5. Changes to the Product Information

As a result of this variation, section 4.2 of the SmPC of Comirnaty 30 microgram/dose is updated to change posology recommendations for booster use from "individuals 18 years of age and older" to "individuals 12 years of age and older". The Package Leaflet (PL) is updated accordingly.

6. Overall conclusion and impact on the benefit/risk balance

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak.

COVID-19 in adolescents is mostly a mild disease. Severe cases occur rarely, and predominantly in subjects with underlying conditions. Several different variants of SARS-CoV-2 have been circulating since the outbreak started, with the omicron variant being the dominant variant at the present time. Analysis of antibody titres of vaccinated adults have shown that the titres of neutralising antibodies to the omicron variant of SARS-CoV-2 are considerably lower when compared to the titres to the Wuhan-based strain included in the vaccine. Observational data also indicate that in adults the vaccine effectiveness to the omicron variant is lower. This effectiveness to the omicron variant can be increased by administration of a booster dose.

There are currently no vaccines against COVID-19 approved for use as a booster in adolescents.

The current variation concerns extending the booster recommendation to include individuals from 12 years of age. The MAH has submitted a brief clinical overview, three published studies (not sponsored by the MAH) and passive surveillance data from Israel.

The previously submitted data to support the administration of a booster dose were derived from the trial C4591001. No relevant new trial data have been submitted in this variation i.e. the inclusion of adolescents is based on evidence transfer from the existing data on immunogenicity and safety. There are supporting observational data as regards safety.

The published studies provided by the MAH (Arbel et al, Barda et al, Bar-on et al) mainly relate to effectiveness of a booster dose in adults.

The post-marketing data available to the MAH were previously reviewed in the summary safety reports. The latest summary safety report is dated February 04, 2022, where it was concluded that no new safety signal was identified following a booster dose.

The passive surveillance data from the Israeli Ministry of Health contains spontaneously reported adverse events following 1, 2 and 3 doses of Comirnaty in subjects 12-15 years of age. A total of 102,086 subjects had received a third dose. The provided passive surveillance data from Israel do not indicate any new safety concerns.

Myocarditis and pericarditis are identified risks following the vaccination with Comirnaty. Based on epidemiological data across all age ranges above 12 years, a frequency of very rare has been estimated for both events. These events have been observed more often after the second vaccination and in younger males.

The ability of Comirnaty to boost the vaccine-induced immune response has been demonstrated in adults 18 to 55 years of age. Although clinical data of a booster dose use in adolescents was not submitted, it is considered appropriately justified to update section 4.2 of the SmPC of Comirnaty 30 microgram/dose to lower the age of the booster dose from adults 18 years of age and older to adults and adolescents 12 years of age and older. Comirnaty has been shown to be at least as good at inducing neutralising antibody titers after the primary series in adolescents as in adults, and while the ability to boost the vaccine-induced immune response was only shown in adults, a booster response to the vaccine can be equally expected in adolescents.

Further, in view of the overall similarity of the safety profile of the primary vaccine regimen between adolescents and healthy adults, and the fact that the booster dose in adults is not more reactogenic than the second dose, it can be extrapolated that no particular safety concerns with the booster dose in adolescents are to be expected. This is confirmed by the submitted safety information from the Israeli Ministry of Health showing that after administering a single booster dose to more than 6,000 12- to 15-year-olds, no new safety concerns were identified through 15 December 2021.

It has been shown in adults that the administration of a booster dose is able to induce titres of neutralising antibodies. Observational data confirm that effectiveness against symptomatic disease due to the omicron variant can indeed be increased by the booster injection. Based on the above, it is justified that if protection induced by the primary schedule needs to be recovered in adolescents, due to either waning antibodies or emergence of new variants, a booster dose can be administered. There are no reasons to believe that the administration of a booster to adolescents 12-17 years results in antibody titres that are inferior to the titres observed in adults.

Entirely new safety concerns are not anticipated, given the large available experience with this vaccine.

Further data will be submitted for assessment in the remit of the PSURs and summary safety reports as well as the substudies B and C from study C4591031.

The benefit-risk balance of COMIRNATY, remains positive.

7. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 4.2 of the SmPC of Comirnaty 30 microgram/dose in order to change posology recommendations for booster use from "individuals 18 years of age and older" to "individuals 12 years of age and older", based on real world evidence collected by the Ministry of Health of Israel and published literature data. The Package Leaflet is updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes throughout the product information.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

[i] Israel Ministry of Health. Corona Vaccine Safety Follow-up. 15 December 2021. Available at: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_vaccine-safty-15122021.pdf. Accessed 29 December 2021.