



REQUEST FOR PRIORITY REVIEW

COVID-19 Vaccine (BNT162, PF-07302048)

sBLA 125742/45

DECEMBER 2021

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CFR	case fatality rates
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
GMFR	geometric mean-fold rise
GMT	geometric mean titer
ICU	intensive care unit
IM	intramuscular(ly)
IND	Investigational New Drug
IQR	interquartile range
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome Coronavirus-2; virus causing the disease COVID-19
sBLA	supplemental Biologics License Application
SOC	System Organ Class
US	United States
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	Variant of Concern
VOI	Variant of Interest
WHO	World Health Organization

1. OVERVIEW

In accordance with the provisions outlined in the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration (FDA) Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)¹, Pfizer and BioNTech are requesting Priority Review Designation for the expansion of licensure of BNT162b2 (COMIRNATY) to individuals 12-15 years of age. BNT162b2 is a prophylactic vaccine that targets severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19). The proposed expanded indication for the candidate vaccine is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥ 12 years of age. The proposed dosage is 30 μg via intramuscular (IM) injection following a dosing regimen of two 0.3-mL doses given 3 weeks apart. The Investigational New Drug Application (IND 19736) for BNT162b2 was effective on 29 April 2020. Emergency use authorization (EUA 27034) for active immunization to prevent COVID-19 caused by SARS-CoV-2 was initially issued for BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) on 11 December 2020 for individuals 16 years of age and older. Emergency use authorization was extended to individuals 12 through 15 years of age on 10 May 2021. BNT162b2 was licensed for use in individuals 16 years of age and older on 23 August 2021 (BLA 125742). The BLA was granted Priority Review Designation. Pfizer and BioNTech are presently seeking expansion of licensure of BNT162b2 to include individuals 12-15 years of age and are requesting priority review.

1.1. Rationale for Priority Review

The supplemental Biologics License Application (sBLA) for BNT162b2 meets the criteria for priority review designation, as outlined in the 2014 *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, because BNT162b2 prevents a serious and life-threatening condition (COVID-19) in individuals 12-15 years of age and, if approved, would provide a significant improvement in safety and effectiveness because there are currently no vaccines licensed for the prevention of COVID-19 in the US for this age group (Section 1.2 and Section 1.4).¹

1.2. Serious and Life-threatening Disease

1.2.1. Background and Clinical Presentation of COVID-19

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, and on 11 March 2020 the World Health Organization (WHO) characterized the COVID-19 outbreak as a pandemic. At the time of this submission, the ongoing pandemic remains a significant challenge to public health and economic stability worldwide, for which for a licensed prophylactic vaccine is a necessary and critical mitigation.

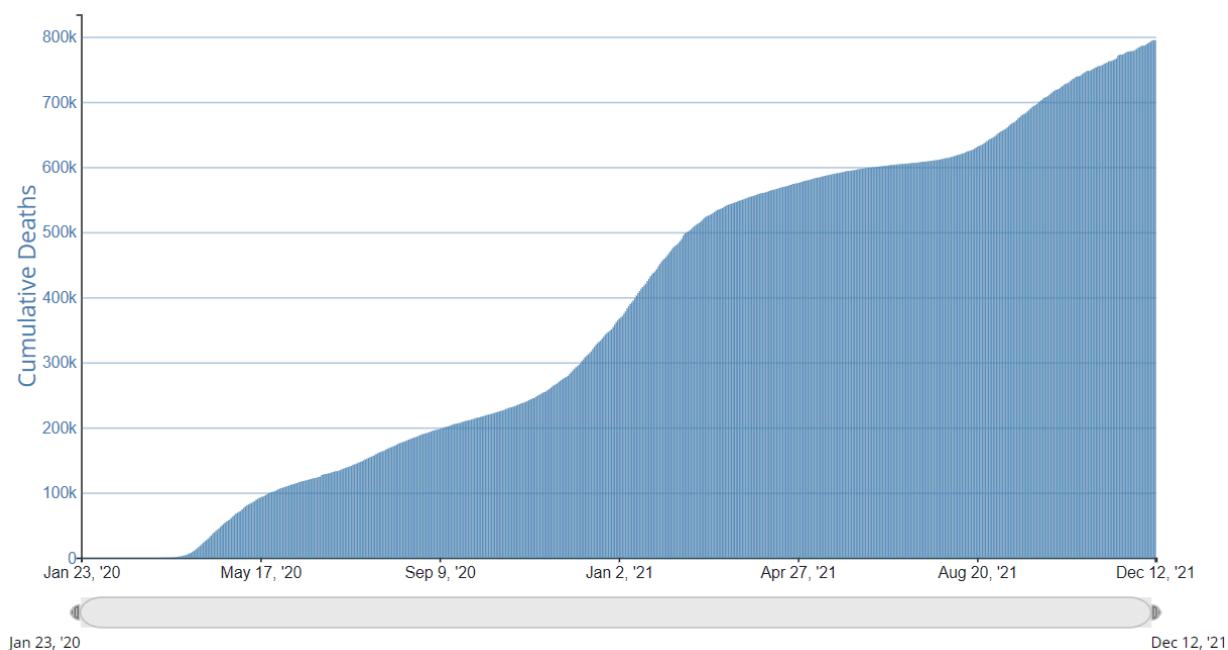
COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing.² However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.²

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, and rhinorrhea.² Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.²

The US Centers for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:³ fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting, fatigue, headache, nasal congestion or runny nose, or nausea.

All ages may present with the disease, with case fatality rates (CFR) elevated in persons >60 years of age.⁴ Comorbidities are associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease.⁵ Healthcare workers are over-represented among COVID-19 patients due to occupational exposure to infected patients.⁵ In the US, the death total has risen to almost 800,000 as of 12 December 2021 (Figure 1).⁶

Figure 1 Trends in Total Deaths in The United States Reported to CDC



1.2.2. Incidence and Prevalence of COVID-19

With the widespread availability of COVID-19 vaccines in the United States, the disease burden has shifted to increasingly impact younger age groups, particularly pediatric and adolescent populations who remain largely unvaccinated.⁷ As of the week ending October 16, 2021, the age groups 5-11, 12-15, and 16-17 years had among the highest weekly case rates per 100,000 population (164.1, 154.0, and 163.8 per 100,000, respectively).⁸ Although the hospitalization rate among those 12-17 years of age is low relative to other age groups (1.6/100,000 or lower since October 2021)⁹, among those who are hospitalized, the risk of progression to severe disease (requiring ICU admission, invasive mechanical ventilation, or in-hospital death) in this age group is approximately 30-34%.^{10,11,12}

1.3. Unmet Medical Need

Vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus. Immunization with a safe and effective COVID-19 vaccine is a critical component of the nation's strategy to reduce COVID-19-related illnesses, hospitalizations, and deaths and to help restore societal functioning.

Data from pre-clinical and clinical studies on tolerability, safety, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 Vaccine have shown the known and potential benefits outweigh the known and potential risks for individuals 16 years of age and older, and formed the basis of approval of Pfizer-BioNTech COVID-19 Vaccine in the US. As of December 2021, BNT162b2 30- μ g has received temporary authorization for emergency use, conditional marketing authorization approval, or full approval in >90 countries globally.

Licensure of Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age at this time addresses an urgent public health need. These adolescents have experienced unprecedented prolonged disruption to education and social development for over a year during the SARS-CoV-2 pandemic, due to infection risk in congregate settings; this in turn creates significant challenges for families and communities, in particular where the pandemic has exacerbated pre-existing socio-economic disparities.^{13,14} Education is a key determinant of health and a driver of economic opportunity. Expanding COVID-19 vaccination eligibility to include adolescents, in addition to individuals 16 years of age and older, would further protect communities (eg, support a safe return to in-person learning for schools and increase vaccination rates overall). Licensure of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age, based on demonstrated effectiveness (via immunobridging), efficacy, and safety data from approximately 2200 individuals in this age group in pivotal Study C4591001, would address critical and dual unmet needs for public health and education.

1.4. Significant Improvement in Safety and Effectiveness through Prevention of COVID-19 Disease

1.4.1. Overview of Immunogenicity

Refer to Section 11.3 of the adolescent interim CSR dated 14 April 2021 (through data cutoff date of 13 March 2021, [Module 5.3.5.1 C4591001 Adolescent Interim CSR](#)) for full details of immunogenicity analyses for adolescent participants 12-15 years of age, including results for additional immunogenicity endpoints which were analyzed for SARS-CoV-2 serum neutralizing titers (GMTs, GMFRs, and seroresponse rates).

Immune response to BNT162b2 30 μ g in SARS-CoV-2 50% neutralizing titers in adolescents 12-15 years of age was noninferior to (and in fact exceeded) the immune response in young adults 16-25 years of age, which provides immunobridging for adolescents. Substantial increases over baseline in neutralizing GMTs and high seroresponse rates were observed at 1 month after Dose 2 in both age groups, which were observed for participants with baseline SARS-CoV-2 positive and negative status. The vast majority of BNT162b2 recipients in both age groups achieved a \geq 4-fold rises from before vaccination to 1 month after Dose 2.

1.4.2. Overview of Efficacy – Updated Analysis

Refer to Section 11 of the adolescent 6-month update interim CSR dated 12 December 2021 ([Module 5.3.5.1 C4591001 Adolescent 6-Month Update Interim CSR](#)) for full details of updated efficacy analyses for adolescent participants 12-15 years of age. Descriptive efficacy analyses were conducted for the adolescent group on cases accrued during blinded placebo-controlled follow-up period through the data cutoff date of 02 September 2021.

In the adolescent group, in efficacy analyses in the evaluable efficacy population based on cases reported from at least 7 days after Dose 2 through the data cutoff date (02 September 2021), the estimated VE against confirmed COVID-19 was 100% (95% CI: 86.8%, 100%) for individuals without evidence of prior SARS-CoV-2 infection before and during vaccination regimen, and 100% (2-sided 95% CI: 87.5%, 100%) for those with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen.

Among participants without and with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen (evaluable efficacy population), VE against COVID-19 occurring at least 7 days after Dose 2 was evaluated for demographic and risk subgroups, and the estimated VE was 100.0% for all subgroups.

The efficacy analysis for the Dose 1 all-available (modified intention-to-treat) population, included 3 cases in the BNT162b2 group (all occurring within <11 days after Dose 1 and in participants who had baseline SARS-CoV-2 negative status) and 48 cases in the placebo group, with an estimated VE against all cases occurring at any time after Dose 1 of 94.0% (2-sided 95% CI: 81.3%, 98.8%).

No severe cases were reported in the 12-15 years of age group as of the data cutoff date (02 September 2021).

Most variants sequenced were neither Variant of Interest (VOI) nor Variant of Concern (VOC) except for the B.1.1.7 (Alpha) found in 23.3% of placebo participants. All of the cases in the efficacy analyses occurred between 02 November 2020 to 19 May 2021, which is before the Delta surge in the US.

Overall, these updated efficacy data strongly support BNT162b2 use in adolescents 12-15 years of age.

1.4.3. Overview of Safety

Refer to Section 12 of the adolescent 6-month update interim CSR dated 12 December 2021 (through data cutoff date of 02 September 2021, [Module 5.3.5.1 C4591001 Adolescent 6-Month Update Interim CSR](#)) for full details of updated safety analyses for adolescent participants 12-15 years of age.

Based on Phase 3 data from 2260 participants 12-15 years of age with up to at least 6 months of follow-up after Dose 2 in Study C4591001, BNT162b2 at 30 µg was safe and well-tolerated and aligned with that previously demonstrated for 16 yrs and older. The AE profile did not suggest any new safety concerns. The incidence of SAEs was low in the context of the number of participants enrolled and comparable in the BNT162b2 and placebo groups. Only 1 participant

discontinued from the study due to an AE (related nonserious AE of pyrexia [previously reported]), and there were no deaths.

Cumulative safety follow-up from Dose 1 to 6 months after Dose 2 for 1113 adolescent participants originally randomized to BNT162b2 (comprising the combined blinded placebo-controlled and open-label observational periods), and from the open-label follow-up of 1010 adolescent participants originally randomized to placebo (from the time of unblinding to receive BNT162b2 until the data cutoff date), showed no new safety signals or suggested any new safety concerns arising from this period of follow-up.

Similarly, analyses of new AEs since the EUA data snapshot showed no new safety signals or concerns.

Safety analysis results for subgroups based on demographics (age, race, ethnicity, and sex) and by baseline SARS-CoV-2 status (positive vs negative) have not shown any clinically important differences in the BNT162b2 safety profile.

Adolescent Phase 3 safety data were generally concordant with previously reported adult safety data (≥ 16 years of age) in Phases 1-3 of the study.

1.4.4. Overview of Supportive Real World and Post-Authorization Data Following Use of BNT162b2 in Children 12-15 Years of Age

The Phase 3 Study C4591001 updated efficacy results are supported by contemporaneous real-world data from Israel and the United States demonstrating high vaccine effectiveness (90%) of two doses of BNT162b2 against symptomatic COVID-19 in the adolescent population.^{15,16,17,18,19,20}

Two studies from Israel examined short-term VE against infection up to 3-4 weeks after the second dose among adolescents without prior SARS-CoV-2 infection.^{15,16} Among individuals aged 12-15 years who received their second dose between July 1, 2021 and July 24, 2021 (i.e., during the early stages of the delta variant outbreak in Israel), adjusted VE against infection in the 8-28 days after the second dose was 92% (95% CI: 88-94).¹⁵ Similarly, in another study of adolescents aged 12-18 years vaccinated between June 8-September 14, 2021, a time period when the delta variant accounted for over 95% of all new cases in Israel, VE in the 7-21 days after the second dose was 90% (95% CI: 88-92) against infection and 93% (95% CI: 88-97) against symptomatic COVID-19.¹⁶

Results from two studies reporting VE against infection among US adolescents are remarkably consistent with the results observed in Israel.^{17,18} Among Kaiser Permanente Southern California (KPSC) members aged 12-15 years, the adjusted VE against infection through August 8, 2021 was 91% (95% CI: 88-93). Further, protection against infection remained high through 3 months following the second dose (the latest follow-up available with sufficient sample size for evaluation); adjusted VE at <1 month, 1 to <2 months, and 2 to <3 months was 91% (95%: 86-94), 92% (95% CI: 88-94), and 88% (95% CI: 68-96), respectively.¹⁷ In another US study examining Kaiser Permanente Northwest enrollees during July 4-September 11, 2021, a period of delta predominance, the incidence rate ratio for infection comparing vaccinated (≥ 2 doses)

versus unvaccinated adolescents aged 12-17 years was 8.9 (95% CI: 6.6-11.9), which can be calculated as a VE against infection of approximately 91%.¹⁸

Two CDC studies that assessed protection against hospitalization among the adolescent population reported VE estimates of approximately 90%.^{19,20} Among US patients aged 12-18 years hospitalized at 19 pediatric hospitals across 16 states, adjusted VE against hospitalization during June 1-September 30, 2021 was 93% (95% CI: 83-97). Results were similar when stratified by age group; VE was 91% (95% CI: 74-97) among patients aged 12-15 years and 94% (95% CI: 78-99) among patients aged 16-18 years. The median (interquartile range [IQR]) duration between the second dose and illness onset was 72 (45-97) days.¹⁹ The second study estimated the risk of hospitalization by vaccination status among adolescents aged 12-17 years from June 20-July 31, 2021. This study reported an incidence rate ratio of 10.1 (95% CI: 3.7-27.9), which can be calculated as a VE of approximately 90%. It should be noted, however, that the sample size of this analysis was small (n=68).²⁰

Overall, real-world effectiveness data to date indicate high VE against infection and hospitalization following two doses of BNT162b2 in individuals 12-15 years of age of approximately 90%.

Real-world safety surveillance data has shown that rare cases of post-vaccination myocarditis may occur in individuals 12–15 years of age (21.5 per million second doses administered based on VAERS).²¹ These events tend to occur more frequently after the second dose and among males (39.9 vs 3.9 per million second doses administered in males versus females, respectively).²¹

1.4.5. Overview of Post-authorization Safety Data

Post-authorization safety data are continually monitored by Pfizer and BioNTech for pharmacovigilance and risk management purposes. Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment. Cumulatively, out of the 629,525 total reports received through 30 September 2021, there was a total of 3320 post-marketing reports containing 10,050 events occurred in pediatric individuals aged between 12 and 15 years of age.

Consistent with events in Phase 2/3 of Study C4591001, most reported AEs were in SOCs with reactogenicity events. The SOCs that contained the greatest number ($\geq 5\%$) of events included General disorders and administration site conditions (2545 AEs), Nervous system disorders (1606), Injury, poisoning and procedural complications (1131), Gastrointestinal disorders (830), Skin and subcutaneous tissue disorders (599), Musculoskeletal and connective tissue disorders (584), Respiratory, thoracic and mediastinal disorders (495), Cardiac disorders (362), Investigation (350), Infections and infestations (229), Psychiatric disorders (188) and Vascular disorders (167).

The safety profile of BNT162b2 remains aligned with the approved label. There was no new significant information emerging from the close monitoring for anaphylaxis and myocarditis/pericarditis, and the analyses of cumulative post-authorization safety data, including

a review of AESIs, are consistent with the analysis of the pivotal clinical study (C4591001) and has confirmed the favorable benefit-risk profile of the vaccine.

Further details regarding the cumulative analysis of post-authorization safety data are presented in [Module 5.3.6](#).

1.5. Conclusions

The sBLA meets the criteria for priority review designation, as outlined in the 2014 *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* because BNT162b2 prevents a serious and life-threatening condition (COVID-19) and, if approved, would provide a significant improvement in safety and effectiveness because there are currently no vaccines licensed for the prevention of COVID-19 in the US for individuals 12-15 years of age.¹

The available and updated clinical data for BNT162b2 effectiveness includes induction of strong immune responses and overwhelmingly high vaccine efficacy with a satisfactory safety profile, suggesting that the vaccine confers safe and effective protection against COVID-19 in individuals ≥ 12 years of age.

The potential risks are based on the observed clinical study safety profile to date, which shows low incidence of severe or serious events, and no new clinically concerning safety observations or safety concerns (and mostly mild reactogenicity, as previously reported). The vaccine has been shown to be safe and well-tolerated irrespective of prior infection with SARS-CoV-2. In this adolescent age group, no AEs were reported that suggested any potential cases of severe COVID-19.

The safety profile of BNT162b2 remains aligned with the approved label. There was no new significant information emerging from the close monitoring for anaphylaxis and myocarditis. Review of post-authorization data did not identify any additional or unexpected risks associated with BNT162b2 and confirms the favorable benefit-risk balance observed in the clinical study. Post-marketing surveillance activities will continue.

The currently available evidence on real-world effectiveness strongly supports a positive benefit-risk profile for vaccination of individuals 12–15 years of age with BNT162b2 to protect against COVID-19 and add another important layer of community protection as the US struggles to turn the corner on the pandemic, ensure that the success of the vaccination program achieved to date is not undone, and resume normal life.

Efficacy data suggest highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics including age and prior SARS-CoV-2 infection, with 100% VE observed in adolescents 12-15 years of age.

Overall, the potential risks and benefits in adolescents, as assessed by the updated safety and efficacy profiles of BNT162b2, are balanced in favor of the potential benefits to prevent COVID-19 in immunized individuals 12-15 years of age. Important risks of BNT162b2 are described in the Pharmacovigilance Plan and will continue to be assessed and minimized as described in the updated Pharmacovigilance Plan. The public health impacts that include

individual and community health, education, and socio-economic outcomes also weigh in favor of expediting full licensure of BNT162b2 for immunization of individuals 12-15 years of age.

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