REQUEST FOR PRIORITY REVIEW

COVID-19 Vaccine (BNT162, PF-07302048)

BLA 125742

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ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DART	Developmental and Reproductive Toxicology
EUA	Emergency Use Authorization
FDA	(US) Food and Drug Administration
FIH	first-in-human
GLP	Good Laboratory Practice
GMC	geometric mean concentration
GMT	geometric mean titer
HCS	human convalescent serum
HIV	human immunodeficiency virus
IFNγ	interferon-gamma
IgG	immunoglobulin G
IL-2	interleukin-2
IM	intramuscular(ly)
IND	Investigational New Drug
LTCF	long term care facility
NHP	non-human primate
PDUFA	Prescription Drug User Fee Act
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome Coronavirus-2; virus causing the disease COVID-19
SOC	System Organ Class
US	United States
Th1	helper T cell type 1
VAED	vaccine-associated enhanced disease

Abbreviation	Definition
VE	vaccine efficacy
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 BNT162b2. 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 indication for the candidate vaccine is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 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) for BNT162b2 was effective on 29 April 2020. Fast Track Designation was granted on 07 July 2020 for individuals 18 years of age and older (a copy of the Fast Track Designation Grant Letter is provided in Module 1.7.4). On 11 December 2020, Emergency Use Authorization (EUA 27034) for active immunization to prevent COVID-19 in individuals 16 years of age and older was issued for this vaccine (EUA product identified as Pfizer-BioNTech COVID-19 Vaccine).

1.1. Rationale for Priority Review

Pfizer and BioNTech are seeking US licensure of BNT162b2 for use in individuals ≥16 years of age. The Biologics License Application (BLA) 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) 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 (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]

1.2.2. Incidence and Prevalence of COVID-19

On 25 April 2021, The Center for Systems Science and Engineering at Johns Hopkins University reported more than 146.7 million cases globally, with over 3.1 million deaths from 192 countries/regions. The US (United States) has reported 32 million cases and over 572,000 deaths.[3]

1.3. Unmet Medical Need

There are no vaccines licensed in the US for the prevention of COVID-19 disease.[4]

The FDA issued an EUA for the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine on 11 and 18 December 2020, respectively. An EUA was issued for the Janssen COVID-19 Vaccine on 27 February 2021. These vaccines have been, and continue to be, rigorously tested in large safety and efficacy studies that meet regulatory requirements in the US; however, the EUA places limitations on eligibility and access to the vaccines.

Mass immunization with a safe and effective vaccine against COVID-19 can dramatically alter the trajectory of the pandemic. According to policy briefing by the Institute for Health Metrics and Evaluation published on 31 March 2021, COVID-19 remains a leading cause of death in the US with up to 100,000 additional deaths projected in the US between March and July 2021, many of which can likely be prevented with COVID-19 vaccination.[5,6] Vaccination against COVID-19 began with EUA/conditional approvals in December 2020, in a phased rollout defined by national/regional guidance. However, there continue to be concerning trends that may counteract the impacts of this vaccination effort, including:

- limitations in access to obtaining a vaccine due to infrastructure challenges (ie, clinic and appointment capacity and systems)[7]
- increasing viral transmission fueled by relaxed compliance with mitigations as the pandemic surpasses the 1-year mark (ie, masks, physical distancing, limiting travel)[5,7]
- increasing circulation of emerging variants of concern (which are currently driving continued spread of viral infection in Europe despite extensive mitigation mandates).[5,7]

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

1.4.1. Overview of Nonclinical Data

Key nonclinical evaluations of BNT162b2 included pharmacology (mouse immunogenicity studies, non-human primate [NHP] immunogenicity and challenge studies) and toxicity (two Good Laboratory Practice [GLP] rat repeat-dose toxicity studies) in vitro and in vivo. A developmental and reproductive toxicity (DART) study was completed in rats.

Nonclinical studies in mice and NHP demonstrate that BNT162b2 elicits a rapid antibody response with measurable SARS-CoV-2 neutralizing titers after a single dose and substantial increases in titers after a second dose that exceed titers in sera from SARS-CoV- 2/ COVID-19-recovered individuals. A Th1-dominant T cell response was evident in both mice and NHPs. S-specific CD8+ T cell responses were also detectable in BNT162b2-immunized animals. The

strongly Th1-biased CD4+ T cell response and interferon-γ (IFNγ)+ CD8+ T cell response after immunization with BNT162b2 is a pattern favored for vaccine safety and efficacy and provided added reassurance for clinical safety.[8] In a SARS-CoV-2 rhesus challenge model, BNT162b2 provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological, or histopathological evidence of vaccine-elicited disease enhancement.[9]

Administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week, for a total of 3 weekly cycles of dosing, was tolerated without evidence of systemic toxicity in GLP-compliant repeat-dose toxicity studies.

In a DART study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified mRNA (30 µg) and other ingredients included in a single human dose of BNT162b2 was administered to female rats by the IM route on four occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

In summary, the nonclinical package summarized above supports BNT162b2 administered twice by IM injection at a dose of 30 µg RNA. Additional details of nonclinical studies are provided in Module 2.4.

1.4.2. Overview of Completed and Ongoing Clinical Trials

The COVID-19 vaccine candidate is currently being studied in a global clinical trial (Study C4591001 and other clinical trials under BB-IND 19736, as well as a German clinical trial (Study BNT162-01, not under the IND).

The German first-in-human (FIH) Phase 1/2 study (BNT162-01) was conducted to gather safety and immunogenicity data on several BNT162 vaccine candidates to inform the overall clinical development of a COVID-19 vaccine. Phase 1 of Study C4591001 evaluated 2 vaccine candidates, and safety and immunogenicity results led to the selection of a single candidate, BNT162b2 (30 µg). The first 360 Phase 2/3 subjects comprised the Phase 2 portion of the study; these subjects contributed to efficacy, immunogenicity, and safety endpoints. Study C4591001 is currently in Phase 3 and available results as of the latest data cutoff dates are summarized in the sections below.

Efficacy analyses are event-driven in pivotal Study C4591001 Phase 2/3 participants ≥12 years of age. Prespecified analyses were conducted on 94 confirmed COVID-19 cases (interim analysis data cutoff date: 04 November 2020) and 170 confirmed cases (final analysis data cutoff date: 14 November 2020) reported in participants without prior evidence of SARS-CoV-2 infection before or during the vaccine regimen. Updated analyses of 1165 confirmed cases in blinded placebo-controlled follow-up from Dose 1 to a data cutoff date of 13 March 2021 evaluated duration of protection.

Immunogenicity analyses of adults (18 to 85 years of age) in Study C4591001 include data up to 1 month after Dose 2 in Phase 2, and up to 6 months after Dose 2 in Phase 1.

Safety data are collected cumulatively in Study C4591001. Some participants ≥16 years of age have been unblinded to treatment assignment; therefore, safety data are presented separately for blinded placebo-controlled and open-label periods. Key safety data in the BLA submission include:

- **Blinded placebo-controlled period**: Dose 1 to 1 month after Dose 2 and to unblinding date:
  - Phase 1 participants randomized to BNT162b2 30 µg (to ~6 months after Dose 2)
  - Phase 2/3 participants ≥16 years of age including HIV+ subset (to ~5 months after Dose 2)

- **Open-label observational period**: from unblinding date to data cutoff date:
  - Phase 2/3 participants ≥16 years of age originally randomized to BNT162b2
  - Phase 2/3 participants ≥16 years of age originally randomized to placebo who then received BNT162b2 after being unblinded

- **Cumulative follow-up from Dose 1 to 6 months after Dose 2**: Phase 2/3 participants originally randomized to BNT162b2 (inclusive of blinded data and open-label data), comprised of at least 3000 in each adult age group (16 to 55 years of age, >55 years of age)

Supportive analyses from Study BNT162-01 are provided in this submission for immunogenicity data including T cell responses, and safety data including reactogenicity and adverse events (AEs), for adult participants in the Phase 1 portion of the study.

Further efficacy, immunogenicity, and safety details are summarized in the Clinical Overview in Module 2.5.

1.4.2.1. Safety

1.4.2.1.1. Phase 1 Safety

Based on Phase 1 data from the FIH Study BNT162-01, BNT162b1 and BNT162b2 were safe and well-tolerated in healthy adults 18 to 55 years of age, with no unanticipated safety findings. Reactogenicity and AEs tended to increase in incidence and/or severity with increasing dose of BNT162b2. Reactogenicity was mostly mild to moderate and short-lived after dosing (eg, arose and resolved within the first 1 to 2 days after dosing), and the AE profile and clinical laboratory results did not suggest any safety concerns.

Based on Phase 1 data from Study C4591001 and Study BNT162-01, BNT162b1 and BNT162b2 were safe and well-tolerated in younger healthy adults 18 to 85 years of age, with no unanticipated safety findings. Reactogenicity and AEs were generally milder and less frequent in participants in the older group compared with the younger group and overall tended to increase with increasing BNT162b2 dose. Reactogenicity was mostly mild to moderate and short-lived after dosing, and the AE profile did not suggest any safety concerns, including up to approximately 6 months after Dose 2 for BNT162b2 30 µg groups. Clinical laboratory evaluations showed a transient decrease in lymphocytes that was observed in all age and dose groups after Dose 1, which resolved within approximately 1 week, were not associated with any other clinical sequelae, and were not considered clinically relevant.

Ribonucleic acid (RNA) vaccines are known to induce type I interferon,[10] and type I interferons regulate lymphocyte recirculation and are associated with transient migration and/or redistribution of lymphocytes.[11] This rapid rebound of lymphocytes supports that the lymphocytes are not depleted, but temporarily migrated out of the peripheral blood, and subsequently re-entered the bloodstream by the time of the next assessment.

1.4.2.1.2. Phase 2/3 Safety

Based on Phase 2/3 data from approximately 44,000 participants ≥16 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 across age groups. Reactogenicity and AEs were generally milder and less frequent in participants in the older group (>55 years of age) compared with the younger group (≤55 years of age). Reactogenicity was mostly mild to moderate and short-lived after dosing for both younger and older age groups (ie, median onset between 1 to 4 days after dosing and resolution within 1 to 2 days after onset), and the AE profile did not suggest any serious safety concerns. The incidence of serious adverse events (SAEs) and deaths were low in the context of the number of participants enrolled and comparable between BNT162b2 and placebo. The incidence of discontinuations due to AEs was also generally low and similar between BNT162b2 and placebo groups.

Cumulative safety follow-up to at least 6 months after Dose 2 for approximately 12,000 Phase 2/3 participants originally randomized to BNT162b2, comprising the combined blinded and open-label periods, showed no new safety signals or suggested any new safety concerns arising from longer-term follow-up.

Similarly, open-label follow-up of participants randomized to placebo from the time of unblinding to receive BNT162b2 until the data cutoff date showed no new safety signals or concerns.

Safety analysis results for subgroups based on demographics (age, race, ethnicity) and by baseline SARS-CoV-2 positive versus negative status have not shown any clinically important differences in the BNT162b2 safety profile. Analysis of the subset of individuals with stable human immunodeficiency virus (HIV) did not suggest any safety concerns in this population. Analysis of participants originally randomized to placebo who then received BNT162b2 (Dose 3) by demographic subgroups and based on prior evidence of SARS-CoV-2 infection or prior COVID-19 did not suggest any safety concerns.

Phase 2/3 safety data were generally concordant with safety data in Phase 1 of the study, both overall and with regard to younger and older participants.

1.4.2.2. Efficacy

1.4.2.2.1. Phase 2/3 Efficacy Final Analysis

Evaluable Efficacy Population

In the final efficacy analysis, among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%.

For the second primary endpoint, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 in participants with or without evidence of SARS-CoV-2 infection before and during vaccination regimen was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE greater than 30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%.

Observed VE was very high for the first primary efficacy endpoint across subgroups of age, sex, race, ethnicity, and country, as VE was >93% in all subgroups, with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE).

For the secondary efficacy endpoint analyses, observed VE against confirmed COVID-19 occurring at least 14 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, was 94.2%, with 8 and 139 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE >30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the vaccine efficacy was 88.7% to 97.2%.

Similarly, among participants with or without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after Dose 2 was 94.4%, with 8 and 144 cases in the BNT162b2 and placebo groups respectively. The posterior probability of >99.99% for the true VE >30% met the prespecified success criterion of >98.6% for this endpoint. The 95% credible interval for the vaccine efficacy was 89.1% to 97.3%.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, observed VE of 66.3% against severe COVID-19 occurring at least 7 days after Dose 2 did not meet the prespecified success criterion of the posterior probability >98.6%, due to the small number of severe cases (1 in the BNT162b2 group, 3 in the placebo group) observed after Dose 2 in the study.

The efficacy analyses using Centers for Disease Control and Prevention (CDC) defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

All-Available Efficacy Population

The early onset of protection is readily apparent from cumulative incidence curves, which show that disease onset tracks conjointly for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat after BNT162b2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen) 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (2-sided 95% confidence interval [CI]: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2.

Among the total of 10 severe COVID-19 cases observed after Dose 1, only 1 severe case was seen in BNT162b2 recipients compared to 9 severe COVID-19 cases in placebo recipients; these results, as well as case splits between Dose 1 and Dose 2 and after Dose 2, were consistent with overall efficacy seen against COVID-19. Similar results were observed when using the CDC definition of severe disease.

Overall Conclusions

Final efficacy results show that BNT162b2 at 30 μg provided protection against COVID-19 in participants with or without evidence of prior infection with SARS-CoV-2, including across demographic subgroups, with severe cases observed predominantly in the placebo group.

1.4.2.2.2. Phase 2/3 Efficacy Updated Analysis

Updated Analysis – Efficacy Against Confirmed COVID-19

In the updated descriptive efficacy analysis (data cutoff date: 13 March 2021), among participants in the evaluable efficacy population without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 91.3% (2-sided 95% CI: 89.0%, 93.2%), with 77 cases in the BNT162b2 group and 850 cases in the placebo group. Among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, the estimated VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 91.1% (2-sided 95% CI: 88.9%, 93.0%), with 81 and 873 cases in the BNT162b2 and placebo groups, respectively.

All cases of confirmed COVID-19 are accounted for in the analyses of VE in the Dose 1 all-available (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. In this analysis, the estimated VE against all cases occurring at any time after Dose 1 was 87.8% (2-sided 95% CI: 85.3%, 89.9%), with 131 cases in the BNT162b2 group and 1034 cases in the placebo group.

In this same Dose 1 all-available (modified intention-to-treat) population, the estimated VE against all cases occurring ≥7 days after Dose 2 was 91.2%. The estimated VE was 91.7% from ≥11 days after Dose 1 to before Dose 2, 96.2% for cases occurring from ≥7 days after Dose 2 to

<2 months after Dose 2, 90.1% for the period from ≥2 months to <4 months after Dose 2, and 83.7% for the period ≥4 months after Dose 2.

Efficacy in Subgroups

Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen (efficacy evaluable population), VE against COVID-19 occurring at least 7 days after Dose 2 was evaluated for demographic and risk subgroups, as follows:

- Estimated VE was ≥90% in most demographic subgroups, similar to 91.3% overall VE.

- High estimated VE was observed across age subgroups:
  - 100.0% in participants 12 to 15 years of age
  - 90.6% in participants 16 to 64 years of age
  - 94.5% in participants ≥65 years of age
  - 96.2% in participants ≥75 years of age.

- Estimated VE by country was 86.5% in Argentina; 86.2% in Brazil; 92.6% in the US; and 100.0% in South Africa, Germany, and Turkey.

The estimated VE was similar for participants at risk (91.6%) and those not at risk (91.0%). The estimated VE for participants ≥65 years of age who were at risk was 91.8%, as compared with 98.1% for those ≥65 years of age and not at risk. The estimated VE was similar in obese (91.6%) and non-obese (91.1%) participants. When evaluated by type of comorbidity, the estimated VE was >85% for participants with each comorbidity evaluated, including any malignancy, cardiovascular disease, chronic pulmonary disease, diabetes, obesity, and hypertension.

Efficacy Against Severe Disease

Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen (evaluable efficacy population), the estimated VE against FDA-defined severe COVID-19 (protocol definition) occurring at least 7 days after Dose 2 was 95.3% (2-sided 95% CI: 71.0%, 99.9%), with 1 and 21 cases in the BNT162b2 and placebo groups, respectively. Similarly, the estimated VE was also 95.3% (2-sided 95% CI: 70.9%, 99.9%) among participants with or without evidence of SARS-CoV-2 infection, also with 1 and 21 cases in the BNT162b2 and placebo groups, respectively.

Among participants without evidence of SARS-CoV-2 infection before and during the vaccination regimen (evaluable efficacy population), the estimated VE against CDC-defined severe COVID-19 occurring at least 7 days after Dose 2 was 100.0% (2-sided 95% CI: 88.1%, 100.0%), with 0 and 32 cases in the BNT162b2 and placebo groups, respectively. Similarly, the estimated VE was also 100.0% (2-sided 95% CI: 88.0%, 100.0%) among participants with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, also with 0 and 32 cases in the BNT162b2 and placebo groups, respectively.

Among participants in the Dose 1 all-available (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen, the estimated VE against

FDA-defined severe cases of COVID-19 occurring at any time after Dose 1 was 96.7% (2-sided 95% CI: 80.3%, 99.9%), with 1 case of severe COVID-19 in the BNT162b2 group compared to 30 cases in the placebo group.

1.4.2.3. Immunogenicity

1.4.2.3.1. Phase 1 Immunogenicity

Study BNT162-01 provides evidence for robust T cell-mediated immunity, with antigen induced interferon-gamma (IFNγ) expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of either BNT162b1 or BNT162b2. Immunogenicity data from Study BNT162-01 were generally concordant with results in pivotal Study C4591001, showing robust SARS CoV-2 neutralization following the second dose and complimentary T cell immune response data for both younger and older adults. The durability of T cell responses to BNT162b2 vaccination was evident from maintenance of the Th1 phenotype and persistent IFNγ and IL-2 production by CD4+ and CD8+ T cells up to approximately 6 months.

In Study C4591001, both BNT162b1 and BNT162b2 elicited robust SARS-CoV-2 neutralizing antibody response starting from 7 days after Dose 2 in younger and older adults. Responses were generally stronger in younger adults than in older adults. Neutralizing antibody response was maintained through Day 52 and was similar for the candidates within the corresponding age and dose groups. Comparisons of SARS-CoV-2 neutralizing titers for both vaccine candidates with a panel of HCS support the benefit of a two-dose vaccine regimen with a dose response up to 30 µg.

For the groups that received BNT162b2 at 30 µg, persistence of the immune response was observed through 6 months after Dose 2. SARS-CoV-2 serum neutralizing titers and serum S1-binding IgG concentrations at 6 months after Dose 2 had decreased relative to those observed at 1 month after Dose 2 but remained above pre-vaccination and placebo levels.

The Phase 1 immunogenicity data from both the pivotal and supportive study collectively showed robust immunogenicity elicited by BNT162b2 in both younger and older adults at the 30 µg dose level, which was ultimately selected to proceed to Phase 2/3 development.

1.4.2.3.2. Phase 2 Immunogenicity

Based on immunogenicity results from 360 participants in Phase 2 of Study C4591001, BNT162b2 at 30 µg elicited robust SARS-CoV-2 neutralization and S1-binding IgG antibody responses at 1 month after Dose 2 similar to those previously observed in Phase 1 of the study. Notably, SARS-CoV-2 neutralizing titers were higher in the younger adult compared to the older adult cohort. Of note, geometric mean titers (GMTs) for younger and older participants at 1 month after Dose 2 were comparable to the GMTs of a comparative panel of human convalescent serum (HCS). S1-binding geometric mean concentrations (GMCs) were generally higher in the younger age cohort compared to the older age cohort, again concordant with observations in the Phase 1 portion of the study.

1.4.3. Vaccine Effectivness

Recent data have confirmed effectiveness of BNT162b2 in the real world: in a nationwide study among individuals aged >16 years in Israel (population 9.1M) reported VE at >7 days after

second dose was 95.3% (95% CI 94.9-97.7%) and at >14 days after second dose was 96.5% (95% CI 96.3-96.8%)[12]; in a prospective cohort of healthcare workers in the United Kingdom, which reported VE at >7 days after second dose of 86% (95% CI 76-97%)[13]; in a retrospective nationwide registry study of healthcare workers in Denmark, which reported VE at >7 days after second dose of 90% (95% CI 82-95%)[14]; in a test-negative case control study of individuals aged >80 years in England, which reported VE at >14 days after second dose of 89% (95% CI 85-93%)[15]; in a retrospective cohort study of long term care facility (LTCF)-residents after an COVID-19 outbreak in a LTCF in Kentucky caused by SARS-CoV-2 variant R.1 with the E484K mutation, which reported VE at >7 days after second dose of 64.4% (95% CI 38.5-79.5)[16]; in a retrospective registry study of individuals aged 18-64 years in Sweden, which reported VE at >7 days after the second dose of 86% (95% CI 72-94%).[17]

1.4.4. 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. Through 28 February 2021 (data lock point aligned with Pharmacovigilance Plan), there were a total of 42,086 case reports (25,379 medically confirmed and 16,707 non-medically confirmed) containing 158,893 events. Cases were received from 63 countries.

Consistent with what was seen in Phase 2/3 of Study C4591001, most reported AEs were in System Organ Classes (SOCs) with reactogenicity events: general disorders and administration site conditions (51,335), nervous system disorders (25,957), musculoskeletal and connective tissue disorders (17,283), and gastrointestinal disorders (14,096). Post-authorization data have also informed the addition of adverse drug reactions (ADRs) related to the experience of reactogenicity to the product labeling.

Aside from addition of anaphylaxis and hypersensitivity, the analyses of cumulative post-authorization safety data, including a review of adverse events of special interest (AESIs), are consistent with the analysis of this pivotal clinical trial. Review of post-authorization data has not revealed any novel safety concerns, except for anaphylaxis, 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 BLA for BNT162b2 fulfills the criteria for priority review designation. 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.

The available clinical evidence for BNT162b2 (30 µg) effectiveness includes induction of strong immune responses and overwhelmingly high vaccine efficacy, suggesting the vaccine confers protection against COVID-19 in individuals ≥16 years of age.

The potential risks are based on the observed safety profile to date, which shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations or safety concerns. The vaccine appears to be safe and well-tolerated across the safety population comprising approximately 44,000 study participants ≥16 years of age, among whom approximately 12,000 have been followed for at least 6 months after completing the two-dose regimen. Safety analyses have also included demographic subgroups based on age, sex, race, ethnicity, and baseline SARS-CoV-2 status and the subset with stable HIV. The confinement of severe cases of COVID-19 predominantly to the placebo group versus the BNT162b2 group suggests no evidence of vaccine-associated enhanced disease (VAED). Post-authorization safety review reinforces that BNT162b2 is safe and tolerable.

Vaccine efficacy was remarkably high, ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those with or without prior infection, in the prespecified interim and/or final analyses. Updated analyses with all confirmed cases accrued up to approximately 6 months after Dose 2 showed persistence of protection with estimated VE of ≥91.1%. Overall, observed VE was >90% across subgroups identified by age, sex, race, ethnicity, country, and risk factors and remained high in the updated analysis. Severe cases have been confined overwhelmingly to the placebo group in all efficacy analyses. Efficacy data suggest highly effective protection against COVID-19 in a broad population of individuals across demographic characteristics, with durable immune responses and protection from COVID-19 disease observed up to approximately 6 months after completing the vaccination regimen.

A vaccine program must be implemented expediently and rapidly expanded to have a significant impact on the pandemic course.[6,18] Licensure of BNT162b2 is likely to enhance vaccine uptake by facilitating supply of vaccine from Pfizer/BioNTech directly to pharmacies and healthcare providers/facilities. The greatest impact of BNT162b2 licensure may be direct supply to healthcare providers who serve vulnerable populations such as elderly patients and those who live in rural and underserved communities (ie, individuals who might be unable to navigate the challenges of securing vaccine access using the systems in place for EUA). Expansion of vaccine via licensure would ultimately improve the prospect of achieving population herd immunity to bring the pandemic under control.[19]

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