The BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA) supplement
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Supervisory Concurrence	(b) (6) VRR/CBER (b) (6) BER (b) (6) OVRR/CBER
Applicant	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	COMIRNATY
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.3 mL dose contains 30ug modified mRNA encoding SARS-CoV-2 spike glycoprotein, encapsulated in lipid nanoparticles (LNP)
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular (IM) injection
Dosing Regimen	One 0.3 mL dose
Indication(s) and Intended Population(s)	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AECI	adverse events of clinical interest
AESI	adverse events of special interest
aEUA	emergency use authorization amendment
BLA	biologics license application
BNT162b2	name of the investigational product prior to authorization or approval
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
COMIRNATY	Any formulation of the approved product, Comirnaty, irrespective of strain composition or valency
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019
CR	complete response
CSR	clinical study report
(b) (6)	(b) (6)
DNS	data not shown
ECMO	extracorporeal membrane oxygenation
eCTD	electronic common technical document
ELISA	enzyme-linked immunosorbent assay
EUA	emergency use authorization
ES	executive summary
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFRNT	fluorescent focus reduction neutralization test
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
GRMP	good review management principles
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IM	intramuscular
IS	injection site
ISE	integrated summary of efficacy
ITT	intent-to-treat
LB	lower bound
LL	lower limit
LLOQ	lower limit of quantification
LNP	lipid nanoparticles
MI	myocardial infarction
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
mITT	all-available immunogenicity population
NAAT	nucleic acid amplification test
NDA	new drug application
NME	new molecular entity

NT50	50% neutralizing titer
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PD	protocol deviation
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PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
RMS/BLA	regulatory management system for the biologics license application
RTF	refuse to file
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
sBLA	supplemental biologics license application
U.S.	United States
VAED	vaccine-associated enhanced diseases
VAERD	vaccine-associated enhanced respiratory disease
VOC	variant of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
1M PD2	1-month post-Dose 2
2019-nCov	novel coronavirus 2019
3W PD1	3 weeks post-Dose 1

1. EXECUTIVE SUMMARY

BioNTech Manufacturing GmbH, Inc. and Pfizer, Inc. in partnership (the Applicant) submitted a supplemental Biologics License Application (sBLA) to support licensure for a single dose of Comirnaty (2023-2024 Formula), indicated for active immunization to prevent coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in individuals 12 years of age and older (hereafter ≥12 years of age), irrespective of prior COVID-19 vaccination status. COMIRNATY[1] is a nucleoside modified messenger RNA (mRNA) vaccine that encodes for the prefusion stabilized full-length spike (S) protein of SARS-CoV-2. The original formulation of COMIRNATY, hereafter referred to as Comirnaty (Original monovalent), encoded the S protein of Wuhan-HU-1 SARS-CoV-2 strain (hereafter referred to as the Original strain). Comirnaty (Original monovalent) was referred to in clinical development as BNT162b2[2] and was initially authorized under Emergency Use Authorization (EUA), on December 11, 2020, as Pfizer-BioNTech COVID-19 Vaccine and subsequently licensed on August 23, 2021, for use as a 2-dose primary immunization series (30 µg each, 3 weeks apart) in individuals 16 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was also authorized under EUA for primary series vaccination of individuals 6 months through 15 years of age. Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was also previously authorized for booster vaccination of individuals 5 years of age and older; however, following emergence of the Omicron variant and its sublineages (most recently BA.4/BA.5 and related sublineages) and observations of decreased vaccine effectiveness against Omicron sublineages compared with the Original strain, formulations of the vaccine containing Omicron components were developed to improve vaccine effectiveness. On August 31, 2022, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) also referred to as BNT16b2, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 12 years of age and older, with concurrent revision of the authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) to no longer include use in the U.S. as a booster dose in individuals 12 years of age and older. On October 12, 2022, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 5 years through 11 years of age, with concurrent revision of the authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) to no longer include use in the U.S. as a booster dose in individuals 5 years through 11 years of age. On December 8, 2022, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a third primary series dose in individuals 6 months through 4 years of age, with concurrent revision of the authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) to no longer include its use in the U.S. as a third primary series dose individuals 6 months through 4 years of age. Finally, on March 14, 2023, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months through 4 years of age to provide a single booster dose at least 2 months after completion of primary vaccination with 3 doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent).

On April 18, 2023, FDA authorized the use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in all individuals 6 months of age and older, with a simplified

[1] COMIRNATY refers to any formulation of the approved product, Comirnaty, irrespective of strain composition or valency.
[2] BNT16b2 and variants thereof [e.g., BNT126b2 (Original), BNT16b2, Bivalent (Original and Omicron BA.4/BA.5), BNT16b2 bivalent (B.1.1.7 + B.1.617.2)] refer to the investigational product prior to authorization or approval.

dosing schedule for use of a single dose in individuals 6 years of age and older, irrespective of prior COVID-19 vaccination status; for individuals 6 months through 4 years, a 3-dose primary series is administered to those who are COVID-19 vaccine naïve, and 1 or 2 doses are administered to those who have received one or more previous doses of a Pfizer-BioNTech COVID-19 Vaccine (see FDA Review Memorandum Dated April 18, 2023). The EUA actions removed authorization for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for use in the U.S.

On June 15, 2023, the 182nd Meeting of Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened and recommended an update to the COVID-19 vaccine composition to a monovalent XBB-lineage vaccine. Based on the totality of the evidence presented at the meeting, for the 2023-2024 Formula of COVID-19 vaccines in the U.S., FDA has advised manufacturers seeking to update their COVID-19 vaccines that they should develop vaccines with a monovalent XBB.1.5 composition. With the submission of this sBLA, the Applicant has included nonclinical data to support the update in Comirnaty composition to a monovalent XBB.1.5 formulation, hereafter referred to as Comirnaty (2023-2024 Formula).

This sBLA contains results from 4 clinical studies (studies C4591044, C4591031, C4591001 and BNT162-17). Each of these studies had prespecified immunological endpoints with adequate success criteria to support inferring effectiveness through immunobridging in subjects 12 years of age and older. Comparison of the neutralizing antibody responses induced by bivalent BNT162b2 vaccines with the neutralizing antibody responses induced by BNT162b2 (Original), the latter using the dosing regimen that had demonstrated clinical efficacy, provides, in part, the evidentiary standard to approve the Comirnaty (2023-2024 Formula) BLA.

Safety and effectiveness of a single dose (30 µg) of COMIRNATY including Comirnaty (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older are based on the data from following studies.

Three studies evaluated a single dose in previously vaccinated individuals ≥12 years of age:

- Study C4591044 was the main study to support the safety and immunogenicity of a single dose of BNT162b2, Bivalent (Original and Omicron BA.4/BA.5) in individuals ≥12 years of age who were previously vaccinated with BNT162b2 (Original monovalent).
- Studies C4591031 and C4591001 provided SAEs and AESIs that FDA reviewed as supportive safety data following Dose 3 of BNT162b2 (Original) in BNT162b2 (Original)-experienced individuals ≥16 years of age (5081 vaccine, 5044 saline placebo) and individuals 12-15 years of age (n=825), respectively.
- Study C4591001 also contributed immunogenicity data in a subset of 268 participants 18-55 years of age following BNT162b2 Dose 3. The safety and immunogenicity with BNT162b2, Bivalent (Original/Omicron BA.4/BA.5) and BNT162b2 (Original monovalent) are pertinent because these vaccines are manufactured using a similar process as Comirnaty (2023-2024 Formula).

Safety and effectiveness of a single dose (30 µg) of COMIRNATY including Comirnaty (2023-2024 Formula) in previously unvaccinated, seropositive individuals 12 years of age and older are based on the data from the following study that evaluated a single dose in previously unvaccinated, seropositive individuals ≥18 years of age:

- Study BNT162-17 provided immunogenicity data to support single dose use in individuals ≥18 years of age who were previously COVID-19 vaccine-naïve and had evidence of SARS-CoV-2 infection (seropositive) prior to study vaccination. Neutralizing

antibody responses in COVID-19 vaccine naïve seropositive individuals 12-17 years of age were extrapolated from antibody response in Study BNT162-17 participants ≥18 years of age.

Summary of the four clinical studies:

1. Study C4591044 is an ongoing, randomized, active-controlled, Phase 2/3 study to evaluate the safety and immunogenicity of bivalent BNT162b2 vaccine candidates as a second booster dose (Dose 4) in COVID-19 vaccine–experienced individuals ≥12 years of age. As of the data cutoff date of October 31, 2022, the median safety follow-up post-Dose 4 was 1.5 months for 528 participants ≥12 years of age (Cohort 2) and 410 participants ≥18 years of age (Cohort 3), who were enrolled between July 26, 2022, to October 12, 2022, and October 31, 2022, respectively. The primary and secondary objectives were met in participants with and without evidence of prior SARS-CoV-2 infection, as follows:
   - For participants >55 years of age, evaluations of SARS-CoV-2 GMTs and seroresponse rates against the B.1.1.529 (Omicron BA.4/BA.5) and USA_WA1/2020 reference strains elicited by 30 ug BNT162b2, Bivalent (Original and Omicron BA.4/BA.5) (study 1044) were compared with responses after 30 ug BNT162b2 (Original) (age-matched participants from study 1031 substudy E). The statistical criteria for the primary objectives in participants >55 years of age were met, since the geometric mean ratio (GMR; Bivalent BA.4/BA.5 divided by BNT162b2) of neutralizing antibody titers against Omicron BA.4/BA.5 was 2.91 (LL of 95% CI: 2.45), demonstrating statistical superiority based on a lower bound of the 95% CI >1.0, and the seroresponse rate percentage difference (Bivalent BA.4/BA.5 minus BNT162b2) evaluating seroresponse from pre-study intervention to 1-month after study intervention against Omicron BA.4/BA.5 was -3.03% (LL of 95% CI: -9.68%), demonstrating statistical noninferiority based on a lower bound of the 95% CI >−10%; the criteria for the secondary endpoint was also met, since the GMR against the reference strain was 1.38 (LL of 95% CI: 1.22), demonstrating statistical noninferiority based on a lower bound of the 95% CI >0.67 and a point estimate ≥0.8.
   - For Study C4591044 participants 18-55 years of age the primary endpoints were met compared with responses in Study C4591044 participants >55 years of age, based on noninferiority comparisons of the GMR and percentage of seroresponse rates using the USA_WA1/2020 reference strain.

2. Study C4591031 was a Phase 3 study to evaluate BNT162b2 (Original) boosting strategies in individuals previously vaccinated with BNT162b2. The study was ongoing at the time the sBLA was submitted. In Substudy A, a total of 10,125 participants ≥16 years of age (BNT162b2 (Original), n=5081, placebo, n=5044) received Dose 3 of BNT162b2 (Original), 30 µg at least 6 months after completing a 2-dose 30 µg BNT162b2 (Original) series. As of the data cutoff date, February 8, 2022, 98.9% of participants had completed the 6-month safety follow-up after Dose 3. The median blinded follow-up time after study vaccination was 2.9 months (0.4, 7.5). The duration of follow-up from Dose 3 vaccination to the cutoff date was a median time of 7.1 months (1.0, 8.0). In Substudy C, 65 participants 12-17 years of age received Dose 3 of BNT162b2 (Original), 30 µg at least 5 months after completing a 2-dose 30 µg BNT162b2 (Original) series. The interim clinical study report (CSR) contained 1-month safety follow-up data to the cutoff date July 14, 2022; all 65 participants completed the 1-month post-Dose 3 follow-up visit. Review of serious adverse events (SAEs) and adverse events of special interest (AESIs) following Dose 3 BNT162b2 (Original) vaccination in participants ≥12 years of age did not identify

any new safety concerns compared to events after the primary series. See Appendix A for AESIs.

3. Study C4591001 was a Phase 1/2/3 study of SARS-CoV-2 RNA vaccine candidates, initiated in April 2020. In the booster portion of this study, a BNT162b2 (Original) booster (Dose 3) was evaluated in two age groups (12-15 and 18-55 years of age) separately. The study was ongoing at the time the interim reports for each age group was being prepared. As of the data cutoff date (November 3, 2022), 86.9% of the 825 participants 12-15 years of age had safety follow-up ≥6 months after 30 µg BNT162b2 (Original) Dose 3, with a median follow-up time of 9.5 months (range: 1.5 to 10.7 months). Among BNT162b2 (Original)-experienced participants without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 3, the SARS-CoV-2 50% neutralizing titer (NT50) immune response for the reference strain was noninferior to 1-month post-Dose 2 (GMR: 3.26 [2-sided 97.5% CI: 2.76, 3.86], n=212). Among BNT162b2 (Original)-experienced participants without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 3 was noninferior (10% noninferiority margin) to 1-month post-Dose 2 based on the difference in percentages of participants with seroresponse (4.5% [2-sided 97.5% CI: 1.0%, 7.9%], n=200). Clinical review of AEs and SAEs following BNT162b2 (Original) Dose 3 did not identify any new safety concerns compared with events following the primary series. Lymphadenopathy occurred in 8 (1.0%) participants following BNT162b2 (Original) Dose 3, which was similar to the frequency reported after the 2-dose primary series (0.8%). No participants reported myocarditis or pericarditis. As of the data cutoff date (November 22, 2021), >95% of the 306 participants 18-55 years of age completed the 6-month safety follow-up visit after 30 µg BNT162b2 (Original) Dose 3. From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, the most frequently reported unsolicited AE assessed by the study investigator as related to Dose 3 vaccination was lymphadenopathy (5.2%). The percentage of participants reporting SAEs within 6 months after Dose 3 vaccination were low (≤0.7%), and all SAEs were assessed by the study investigator and FDA as not related to study intervention.

4. Study BNT162-17 was conducted to evaluate the safety and immunogenicity of modified SARS-CoV-2 monovalent and bivalent vaccines. The Applicant conducted a post-hoc analysis of immunogenicity data from this study to address the single dose use in COVID-19 vaccine-naïve seropositive individuals. Immunobridging of the efficacy originally demonstrated in Study C4591001 was done by comparison of the USA_WA1/2020 reference strain immune response in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection at 3 weeks after the single dose of bivalent BNT162b2 (Alpha/Delta) with the immune response at 1-month after 2 doses of the BNT162b2 (Original) vaccine in participants without evidence of prior infection. This analysis demonstrated that in individuals 18-85 years of age, a single dose of bivalent BNT162b2 (Alpha/Delta) in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection could be expected to have at least noninferior efficacy to 2 doses of the BNT162b2 (Original) vaccine in participants without evidence of prior infection based upon: 1) noninferiority of the reference strain immune response based on geometric mean ratio (GMR); and, 2) noninferiority of reference strain immune response by difference in percentage seroresponse rate (exceeded the noninferiority margin by 0.04%). The totality of these immunogenicity data supports the conclusion that a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in seropositive COVID-19 vaccine-naïve individuals is at least noninferior two doses in seronegative COVID-19 vaccine-naïve individuals.

The clinical data submitted meet FDA's statutory effectiveness standards and safety standards for data to support licensure of vaccines for prevention of COVID-19, including relevant efficacy success criteria and numbers of vaccinated study participants and follow-up time (i.e., at least 3,000 vaccinated participants in each age group with at least 6 months of total safety follow-up) for an acceptable safety database. The totality of the clinical data presented above support the proposed indication for use of COMIRNATY as a single dose (30 µg) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status. The safety and effectiveness of Comirnaty (Original monovalent) and BNT162b2, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Comirnaty (2023-2024 Formula) because these vaccines are manufactured using a similar process. This independent assessment of submitted clinical trial data serve as the basis to support the safety and effectiveness of future periodic strain updates to COMIRNATY.

Pediatric Assessment and Pediatric Research Equity Act
Pediatric studies evaluating a single dose of COMIRNATY in children younger than 12 years of age (<12 years of age), as required by the Pediatric Research Equity Act, were deferred for this application, and will be completed after approval of Comirnaty (2023-2024 Formula) for use as a single dose in individuals ≥12 years of age. The requirement for an assessment of a single dose of COMIRNATY in children 0 to <6 months of age has been waived because there is evidence strongly suggesting that a single dose of COMIRNATY would be ineffective in this age group. The Applicant also committed to conduct a postmarketing study (a PMC study) of immune responses following a single dose of Comirnaty (2023-2024 Formula) in individuals ≥12 years of age who have not been previously vaccinated with a COVID-19 vaccine.

1.1 Demographics

The demographics of study participants across the ongoing Studies C4591044, C4591031, and C4591001 were balanced across the study subgroups. The demographics for the subgroup analysis of Study BNT162-17 were not balanced with those of the comparator group in Study C4591001. Individual study demographics are noted in Section 6 under the subsections for each study.

Effectiveness
In study C4591044, subgroup analyses of vaccine immunogenicity (although limited by small numbers in some subgroups) did not suggest clinically meaningful differences in SARS-CoV-2 neutralizing GMT or seroresponse by sex, ethnicity, race, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19.

Safety
Solicited local and systemic reactions following BNT162b2 (Original) vaccinations were generally lower among older adults (>55 years of age) compared with younger adults and adolescents (12-55 years of age). No clinically meaningful differences were observed in the occurrences of solicited local and systemic reactions were observed by ethnicity, race, sex or baseline SARS-CoV-2 status.

1.2 Patient Experience Data

No patient experience data were submitted in the Application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. As of August 16, 2023, SARS-CoV-2 infection has resulted in over 770 million cases of COVID-19 and an estimated 7 million deaths worldwide (WHO, 2023a). Disease symptoms vary. Many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older and individuals with certain co-morbid conditions (CDC, 2023d), may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2022c). Symptoms associated with SARS-CoV-2 infection in children are similar to those in adults but are generally milder, with fever and cough most commonly reported (Irfan, 2021; Liguoro, 2020). However, since the January 2022 surge in cases due to Omicron BA.1, rates of COVID-19-associated hospitalizations among infants younger than 6 months old are similar to those of adults ages 65 to 74 years old (CDC, 2023e).

In the U.S., more than 6.3 million COVID-19-associated hospitalizations and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC, 2023c). Individuals 65 years of age and older accounted for approximately 14% of cases and 76% of deaths (CDC, 2021a). By contrast, individuals 18 years of age and younger represent 17% of COVID-19 cases and less than 0.3% of deaths (CDC, 2021a). Since the start of the pandemic, surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. COVID-19 vaccines based on the Wuhan-HU-1 strain of SARS-CoV-2 (also referred to as ancestral, reference, or original strain) were launched in the U.S, starting in December 2020. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently the Omicron variant of concern. Bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines were deployed in the U.S. starting in September 2022.

The SARS-CoV-2 Omicron variant has continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by post-vaccination (with Original strain vaccines) and post-infection sera compared to the pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from post-vaccination and post-infection antibody responses. By spring 2023, BQ sublineages were rapidly replaced by

XBB sublineages, both in the U.S. and globally. The XBB parent lineage resulted from a recombination of BA.2.10.1 and BA.2.75 sublineages, highlighting the relevance of recombination in generating new variants of concern. Recombination can occur during virus replication in cells infected by more than one variant.

XBB sublineages have continued to emerge that have accumulated a small number of mutations in the spike N-terminal domain and the receptor binding domain (RBD). The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world, by April. Compared to the parental XBB lineage virus, XBB.1.5 has two amino acid substitutions, G252V and S486P, in the RBD of the SARS-CoV-2 spike protein. These changes may confer additional growth advantage, likely due in part to increased affinity of the spike protein to the ACE2 receptor conferred by the S486P change (Yue, 2023). Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5. The XBB.1.9 variant has the same spike protein sequence as XBB.1.5, but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness (Jiang, 2020; Gao, 2021). Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April 2023 the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared with the parental XBB lineage virus, XBB.1.16 has four spike substitutions, i.e., E180V, G252V, K478R, and S486P. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses rose rapidly in many other countries, including the U.S. Preliminary reports have indicated that no further immune evasion result from these substitutions in the XBB.1.16 spike protein compared with XBB.1.5 (Wang, 2023; Yamasoba, 2023). Overall, XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023; at this time (August 2023), other circulating variants worldwide include XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant variant in the U.S. in late August 2023 was EG.5. EG.5 carries an additional F456L amino acid substitution in the spike protein compared to the parent XBB.1.9.2 subvariant and XBB.1.5. Within the EG.5 lineage, the subvariant EG.5.1 has an additional spike protein substitution Q52H and represents 88% of the available sequences for EG.5 and its descendent lineages (WHO, 2023b).

SARS-CoV-2 evolution is complex and remains unpredictable. Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. Intrinsic viral factors, e.g., mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals. Thus far, the impressive plasticity, especially in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1.1, or XBB.1.5 lineage, as specified.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

2.2.1 FDA-approved therapies for COVID-19

Oral antivirals:
Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), who are:
Hospitalized; or Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Immune modulators:
Olumiant (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra (Tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

2.2.2 Emergency use Authorized Pharmacological Products for Pre-Exposure Prophylaxis of COVID-19, Post-exposure Prophylaxis and/or Treatment of COVID-19

Oral antivirals:
Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies:
Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them (For detail of previously authorized SARS-CoV-2-targeting monoclonal antibodies, please refer to section 2.2.5 of the FDA Review Memorandum Dated April 18, 2023).

Immune modulators:
Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Tocilizumab is authorized for the treatment of COVID-19 in hospitalized pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma:
COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

2.3 Safety and Efficacy of Pharmacologically Related Products

Spikevax, Moderna COVID-19 Vaccine, and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Spikevax (COVID-19 Vaccine, mRNA), manufactured by ModernaTX Inc., is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Spikevax (Original monovalent) contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain.

A bivalent formulation of the vaccine, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), manufactured using a similar process is currently authorized under EUA for administration of a single dose in individuals 6 years of age and older, two doses in those individuals 6 months through 5 years of age previously not vaccinated with a COVID-19 vaccine and a single dose in individuals 6 months through 5 years of age previously vaccinated with Moderna COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

Novavax COVID-19 Vaccine, Adjuvanted
Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals ≥12 years of age, and as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. For additional information on dosing and schedule, please refer to the Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.4 Previous Human Experience with the Product

Pfizer-BioNTech COVID-19 Vaccine was authorized under EUA on December 11, 2020, and subsequently approved under the trade name COMIRNATY on August 23, 2021. Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized under EUA on August 31, 2022. In the U.S., over 404 million doses of Pfizer-BioNTech COVID-19 vaccines have been administered to date (CDC, 2023e).

2.5 Summary of Regulated Activity Related to the Submission

Major sBLA-associated regulatory activities:

a. January 26, 2023: VRBPAC meeting was held to discuss harmonization of vaccine strain composition for all doses, the simplification of the COVID-19 immunization schedules, and the procedures for routine periodic strain selection.
b. April 18, 2023: The EUA of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was amended to simplify the vaccination schedule to a single dose regimen for most individuals. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.
c. June 15, 2023: The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. and the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage.
d. June 22, 2023: the Applicant was provided an information request pertaining to data to support a strain change to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).
e. June-August 2023: Under IND 19736 and this sBLA (STN 125752.276), multiple communications were provided to the Applicant related to the 2023-2024 Formula, single-dose indication, and Pediatric Study Plan for single-dose regimen.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. Please see review memorandum by (b) (6) (b) (6) for additional details regarding the quality of the study datasets.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Sponsor responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical studies C4591001, C4591031, C4591044, and BNT162-17 including compliance with Good Clinical Practice (GCP) as per 21 CFR 312. The informed consent form for each study contained all the essential elements as stated in 21CFR 50.25.

(b) (4) inspections of three clinical sites in studies C4591001, C4591031, C4591044, and BNT162-17 did not identify deficiencies that would affect the integrity of the clinical data submitted in this BLA. Please see review memorandum by (b) (6) (b) (6) for additional details.

3.3 Financial Disclosures

Covered clinical study (name and/or number): C4591001, C4591031, C4591044, and BNT162-17
Was a list of clinical investigators provided? ☑ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 1100
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2 Is an attachment provided with details of the disclosable financial interests/arrangements? ☑ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☑ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1094 Is an attachment provided with the reason? ☑ Yes ☐ No (Request explanation from applicant)

Reviewer Comment*: The Applicant satisfactorily addressed possible study investigator financial interests that could impact clinical data quality*.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer identified no issues that would impact the conclusions of the clinical review. The manufacturing process development, in-process testing, release, and stability testing were reviewed by the CMC reviewer in support of licensure. The Comirnaty Drug Substance (DS) and Drug Product (DP) manufacturing process and controls were approved under the original BLA. This sBLA reviewed the chemistry, manufacturing, and controls changes information pertinent to manufacturing of Comirnaty (2023-2024 Formula). Facility information provided in the sBLA was reviewed and found to be sufficient and acceptable.

4.2 Assay Validation

The good manufacturing practice for the final drug product and the clinical serologic assays were adequate to support licensure as determined by the CBER Product and Assay reviewers.

4.3 Nonclinical Pharmacology/Toxicology

The CBER toxicology reviewer did not identify any safety issues based on the submitted preclinical studies that would impact the conclusions of this clinical review. Please see CBER toxicology review memorandum for further details.

4.4 Mechanism of Action

The nucleoside modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

4.5 Statistical

No major statistical issues which would impact the clinical conclusions were identified by CBER statistical reviewers in this application. The key statistical analyses for safety, immunogenicity, and efficacy were confirmed by CBER statistical reviewers.

4.6 Pharmacovigilance

Pfizer is conducting safety-related post-authorization/postmarketing studies for Pfizer-BioNTech COVID-19 Vaccines, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Pfizer has a pharmacovigilance plan to monitor safety concerns that could be associated with the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula). The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: None.
- Missing information: Use in Pregnancy, vaccine effectiveness, use in pediatric individuals <6 months of age.

The previous important potential risk vaccine-associated enhanced diseases (VAED)/ vaccine-associated enhanced respiratory disease (VAERD) was removed from the list of safety concerns because the available cumulative safety data (clinical trial and postmarketing data) has not substantiated retaining VAED/VAERD as an important potential risk. VAED/VAERD will continue to be monitored through routine pharmacovigilance.

Applicant Pharmacovigilance Activities
The Applicant will perform routine pharmacovigilance for all adverse events in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). Please see Pharmacovigilance review memorandum for further details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

At the January 26, 2023, VRBPAC meeting, the committee discussed harmonization of the strain composition for primary series and booster doses, simplification of the immunization schedule, and periodic updates of COVID-19 vaccine strain composition. Following this meeting, FDA identified evidentiary gaps and the comprehensive data package needed to address those evidentiary gaps to support a simplification of vaccine composition and immunizations schedule. Accumulating evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection, particularly

against severe COVID-19 and hospital admissions. This evidence supports the rationale of administering a single dose of COVID-19 vaccine to individuals seropositive for SARS-CoV-2 from a prior infection, regardless of prior COVID-19 vaccination status. The feasibility of this strategy would therefore depend on the seroprevalence of SARS-CoV-2 in the population. According to the CDC, the seroprevalence of SARS-CoV-2 was estimated to be 98.8%, 97.8%, 97%, and 92.5% in persons aged 16-29 years, 30-49 years, 50-64 years, and ≥65 years, respectively (CDC, 2022a). Among adolescents 12 through 17 years old, children 5 through 11 years old, and 0 through 4 years old, the seroprevalence of SARS-CoV-2 was estimated to be approximately 99%, 97%, and 90%, respectively (CDC, 2022b). Therefore, given the high seroprevalence of SARS-CoV-2 in individuals 12 years of age and older, FDA sought evidence from the Applicant of the safety and efficacy of a single dose (30 µg) of their COVID-19 vaccine in baseline SARS-CoV-2 seropositive individuals, irrespective of COVID-19 vaccination status.

Clinical data from four clinical studies were submitted to this sBLA, in support of single dose use of the COMIRNATY including Comirnaty (2023-2024 Formula) in individuals ≥12 years of age. In individuals who were previously vaccinated with a COVID-19 vaccines, Study C4591044 was the primary study to evaluate the safety and immunogenicity data following a modified variant COVID-19 vaccine; BNT162b2 Bivalent (Original/Omicron BA.4/BA.5) was administered as Dose 4 of COVID-19 vaccine. Additional safety data from Studies C4591031 and C4591001, in which BNT162b2 (Original) was administered as Dose 3, were also provided. The Applicant submitted a post-hoc analysis of immunogenicity data from Study BNT162-17 to evaluate single dose use in vaccine-naïve seropositive individuals; in this study, SARS-CoV-2 monovalent and bivalent RNA-based vaccines were administered to individuals 18-85 years of age. The safety and effectiveness data accrued with BNT162b2 (Original) and BNT162b2, Bivalent are pertinent to COMIRNATY including Comirnaty (2023-2024 Formula) because all these vaccines are manufactured using a similar process.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The primary source of data considered for review of this investigational vaccine were documents submitted to STN 125742/276/0. The following sections were reviewed in support of this application:

Module 1, all sections: Administrative Information and Prescribing Information
Module 2.2 Introduction
Module 2.5 Clinical Overview
Module 2.7.3 Summary of Clinical Efficacy
Module 2.7.4 Summary of Clinical Safety
Module 2.7.6 Synopses of Individual Studies
Module 5.2 Tabular Listing of All Clinical Studies
Module 5.3.5.1 Clinical Study Reports

During the BLA review period, the following amendments containing clinical information were reviewed:

Table 1. Amendments, Supplemental BLA 125742/276, Submitted February 23, 2023

Amendment Number	Submission Date	Description of Contents
7	May 16, 2023	Response to May 9, 2023, IR RE interim Clinical Study C4591044 report and datasets
8	May 17, 2023	Response to May 9, 2023, IR RE previously submitted information and datasets

Amendment Number	Submission Date	Description of Contents
13	June 13, 2023	Response to June 6, 2023, IR RE vaccination schedule and revised USPI
19	June 30, 2023	Response to June 22, 2023, IR RE PVP and PASS
20	June 30, 2023	Response to June 20, 2023, IR RE C4591044 datasets
24	July 21, 2023	Response to June 30, 2023, IR RE revised USPI for 2023-2024 Formula
25	July 25, 2023	Response to May 1, 2023, May 22, 2023, May 24, 2023, and June 2, 2023, IRs RE Study BNT162-17 data to support a single dose in seropositive, vaccine naive individuals 12 years of age and older
26	July 31, 2023	Revised Section 14.1 of the USPI to contain data to support a single dose in seropositive, vaccine naive individuals 12 years of age and older
29	August 2, 2023	Response to July 31, 2023, IR RE PREA assessment requests
30	August 2, 2023	Response to May 1, 2023, May 22, 2023, May 24, 2023, and June 2, 2023, IRs RE eSub Datasets for BNT162-17 single dose data
33	August 10, 2023	Response to August 9, 2023, IR RE Information Request regarding PREA request
38	August 14, 2023	Revised USPI in response comments sent on August 9, 2023
39	August 16, 2023	Response to August 10, 2023, IR regarding data sets
42	August 23, 2023	Response to August 16, 2023, IR regarding financial certification and disclosure for Study BNT162-17
43	August 23, 2023	Response to August 17, 2023, IR regarding proposed postmarketing commitment
47	August 28, 2023	Response to August 18 and 24, 2023, IR's regarding dilutional linearity and precision raw datasets & no FDA form 3455 being submitted to /276.42 RE study BNT162-17
48	August 30, 2023	Response to August 28, 2023, IR RE: milestone dates for study C4591048 SSA & Response to August 29, 2023, IR RE request for a revised indication statement in cover letter RE: strain change and single dose
50	September 1, 2023	Revised USPI in response comments sent on August 31, 2023
52	September 5, 2023	Revised USPI in response comments sent on September 1, 2023
54	September 5, 2023	Response to IR dated September 1, 2023, RE Information Request regarding Study C4591044 participant narratives
55	September 6, 2023	Response to PI labeling comments sent on September 5, 2023
57	September 7, 2023	Acknowledgement of removal of Sections 14.5 and 14.7 from the PI
58	September 7, 2023	Response to September 6, 2023, clinical IR RE Question re: lymphadenopathy narratives

Source: FDA-generated table.
Abbreviations: IR, information request; PASS, post-authorization safety study; PVP, pharmacovigilance plan; RE, regarding; USPI, United States prescribing information

The amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum. The full Prescribing Information was reviewed, and suggested revisions were sent to the Applicant. The revised Prescribing Information is accurate, not misleading, and appropriate for the proposed use of the product.

Supportive information from EUA 27034 and clinical study protocols reviewed under IND 19736 were also referenced during the review cycle.

5.3 Table of Studies/Clinical Trials

Interim reports from three ongoing clinical studies and an ad hoc analysis submitted to support the safety and effectiveness of COMIRNATY including Comirnaty (2023-2024 Formula) were submitted to support approval and licensure of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2).

Table 2. Overview of Clinical Studies

Study Number	Description	BNT162b2 (30 µg) or Bivalent BNT162b2* Phase, N, Country	Placebo (saline) Phase, N, Country	Study Status
C4591001	Phase 1,2,3 randomized, placebo-controlled, observer- blind, safety, immunogenicity, and VE study [only safety data following administration of BNT162b2 Dose 3 COVID-19 dose are presented in this memo]	Phase 2/3: 1131[a] U.S.A: 1131	Phase 2/3: 0	safety follow-up evaluations ongoing at time of submission – study now completed
C4591031	Phase 3 safety and immunogenicity study to evaluate additional dose(s) of BNT162b2 in individuals previously vaccinated with BNT162b2 [For Substudy A, only safety data following administration of BNT162b2 Dose 3 are presented in this memo]	Substudy A Phase 3: 5081[b] Brazil: 580 South Africa: 134 U.S.A: 4367 Substudy C Phase 3: 65 [b] U.S.A: 65	Substudy A Phase 3: 5044 Brazil: 584 South Africa: 134 U.S.A: 4326 Substudy C Phase 3: 0	safety follow-up evaluations ongoing at the time the report was prepared
C4591044	Phase 2/3 randomized, active-controlled study to evaluate safety and immunogenicity of Bivalent BNT162b RNA-based vaccine candidates as Dose 3 in COVID-19 vaccine–experienced individuals	Phase 2/3: 726[c] U.S.A: 726	Phase 2/3: 0	safety follow-up evaluations ongoing
BNT162-17	Phase 2 study to evaluate safety and immunogenicity of SARS-CoV-2 monovalent and multivalent RNA-based vaccines [only immunogenicity data from this study are presented in this memo]	Phase 2: 262[d] South Africa: 253 U.S.A: 9	Phase 2: 0	Completed

Sources: Study C459001 (12–15-year-old group), Adapted from: STN125742/559 c4591001-interim-mth6-pd3-12-15years of age-report-body.pdf Table 7; Study C459001 (18–55-year-old group), Adapted from: Adapted from: STN125742/559 c4591001-interim-booster-mth6-g0-g3-report-body.pdf Table 14; Study C459031, Substudy A, Adapted from STN125742/276/8, c4591031-suba-interim-mth6-report-body.pdf, Table 8; Study C459031, Substudy C, Adapted from STN125742/276, c4591031-ssc-interim-mth1-12-17years of age-report-body.pdf, Table 7; Study C459044, Adapted from STN125742/276, c4591044-interim-c2-c3-mth1-report-body.pdf, Tables 14 and 15; Study BNT162-17, Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 3.
a Phase 2/3: Overall sample is larger, for review purposes safety data was provided for 12-15 year old participants (825) and 18-55 year old participants (306).
b Phase 3, substudy A enrolled individuals ≥16 years of age
c Phase 2/3: enrolled individuals ≥12 years of age (stratified as 12-17, 18-55, and ≥55 years).
d Phase 2: The number presented represents those included in the ad hoc analysis, primary endpoint (Part B, Cohort 6).
* 30µg BNT162b2 (original), 30µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)

5.4 Consultations

5.4.1 Advisory Committee Meetings

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has periodically convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. At the January 26, 2023, VRBPAC meeting on COVID-19 vaccines, FDA stated that it anticipates assessing SARS-CoV-2 evolution at least annually (review of data to commence in the spring of each year) and to convene the VRBPAC in June of each year regarding strain selection for fall vaccination.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the U.S. as of early June 2023. While XBB.1.5 had declined to less than 40% of presumed circulating virus in the U.S., XBB.1.16 was on the rise and XBB.2.3 was slowly increasing in proportion (CDC COVID Data Tracker: Variant Proportions). The trajectory of virus evolution suggested that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolved. Although SARS-CoV-2 continues to evolve, the amino acid sequences of XBB.1.5, XBB.1.16, and XBB.2.3 spike protein appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new amino acid substitutions in the XBB.1.16 spike protein compared to XBB.1.5. By several measures, including escape from antibody neutralization and waning protection, the currently available bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines appear less effective against currently circulating variants (e.g., XBB-lineage viruses) than against previous strains of SARS-CoV-2. The totality of available evidence suggests that an update to the composition of COVID-19 vaccines to a monovalent XBB-lineage vaccine is warranted for 2023–2024.

The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. Sublineages considered by the VRBPAC included XBB.1.5, XBB.1.16, and XBB.2.3. Evidence influencing strain selection discussed by the Committee included virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, pre-clinical immunogenicity studies evaluating immune responses generated by candidate vaccines. The Committee also reviewed manufacturing timelines.

For the 2023-2024 Formula of COVID-19 vaccines in the U.S., the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage. Based on the evidence and other considerations presented, committee members expressed a preference for selection of XBB.1.5 for the 2023-2024 Formula. Based on the totality of the evidence, FDA advised manufacturers seeking to update their COVID-19 vaccines that for the 2023-2024 Formula of COVID-19 vaccines in the U.S. they should develop vaccines with a monovalent XBB.1.5 composition.

5.5 Literature Reviewed

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FDA, Comirnaty, Pfizer-BioNTech COVID-19 Vaccines | FDA

FDA, Janssen, Janssen COVID-19 Vaccine | FDA

FDA, Novavax, Novavax COVID-19 Vaccine, Adjuvanted | FDA

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C4591044

NCT05472038
"An Interventional, Randomized, Active-Controlled, Phase 2/3 Study To Investigate The Safety, Tolerability, and Immunogenicity of Bivalent BNT162b RNA-Based Vaccine Candidates as a Booster Dose in COVID-19 Vaccine–Experienced Healthy Individuals (≥12 years of age)."

Study C4591044 was designed to evaluate bivalent BNT162b2 Omicron vaccine formulations in individuals ≥12 years of age who were previously vaccinated with BNT162b2. The safety and immunogenicity data from this study were initially intended by the Applicant to support use of 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) in individuals ≥12 years of age.

The interim study report contains 1-month safety and immunogenicity data from participants of Cohort 2 who received 30 µg or 60 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine and Cohort 2 and 3 participants who received 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5). Study C4591031 Substudy E (expanded Enrollment – Group 1]) who received 30 µg BNT162b2 Dose 4 was the comparator for some of the vaccine comparisons. Study C4591044 objectives, endpoints, and monitoring presented in this section reflected the results submitted in the interim report. Safety follow-up evaluations through the 6-month post-Dose 4 vaccination are ongoing. Data from Cohort 1 (BNT162b2 vaccine formulations containing BA.1 or BA.2 components) were not provided in the study report.

6.1.1 Objectives

Study objectives with associated endpoints relevant to this sBLA included the following:
Safety

1. Cohort 2: To describe the safety of BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 30 µg given as Dose 4 to BNT162b2 (Original)-experienced participants 12-17, 18-55, and >55 years of age, and BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 60 µg given as Dose 4 to BNT162b2 (Original)-experienced participants 18-55 and >55 years of age.
   Endpoints
   - Local reactions for up to 7 days post-booster vaccination (pain at the injection site (IS), redness, and swelling)
   - Systemic events for up to 7 days post-booster vaccination (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
   - AEs from Dose 3 vaccination through the 1-month post-booster follow-up visit
   - SAEs from Dose 3 vaccination through the 6-months post-booster follow-up visit

2. Cohort 2 and 3: To describe the safety of BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 30 µg given as Dose 4 to BNT162b2 (Original)-experienced participants 18-55 and >55 years of age.
   Endpoints: described in safety objective #1

Primary Immunogenicity

1. To demonstrate superiority of neutralizing antibody GMT and noninferiority of seroresponse rate of the anti-Omicron BA.4/BA.5 immune responses after 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) Dose 4, compared to corresponding responses after 30 µg BNT162b2 Dose 4 (Study 1031), in BNT162b2 (Original)-experienced participants >55 years of age.

2. To demonstrate the noninferiority of anti-Omicron BA.4/BA.5 seroresponse after 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) Dose 4 in BNT162b2 (Original)-experienced participants 18-55 years of age compared to participants >55 years of age.

   For participants >55 years of age (Cohort 2/Group 4 and Cohort 3/Group 2 combined): SARS-CoV-2 neutralizing antibody responses using the Omicron BA.4/BA.5 strain were evaluated by GMRs and seroresponse using the following statistical criteria:
   - GMR,
     - Statistical superiority criterion: the LL of the 2-sided 95% CI for the GMT ratio is >1.
     - Noninferiority criteria: the LL of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.8
   - Seroresponse, noninferiority criterion: LL of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

   For participants 18-55 years of age (Cohort 2/Group 2 and Cohort 3/Group 1 combined): SARS-CoV-2 neutralizing antibody responses using the Omicron BA4/BA.5 strain were evaluated by GMRs and seroresponse using the following statistical criteria:
   - GMR, noninferiority criterion: LL of the 2-sided 95% CI for the GMR is >0.67
   - Seroresponse, noninferiority criterion: LL of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%

   Seroresponse was defined a ≥4-fold increase in post-booster vaccination titer from baseline (before the study vaccination). If the baseline titer was <LLOQ, a post-booster vaccination titer ≥4 × LLOQ was considered a seroresponse.

Secondary Immunogenicity

To demonstrate the noninferiority of the anti–reference strain immune response after BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 30 µg compared to BNT162b2 30 µg given as Dose 4 in BNT162b2 (Original)-experienced participants >55 years of age.

Endpoint: SARS-CoV-2 neutralizing antibody GMT

Statistical Criteria

SARS-CoV-2 reference strain

- GMT ratio, noninferiority criteria: the LL of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥0.8

Exploratory Immunogenicity

To describe the immune response to emerging VOCs (Cohort 2, combined Cohort 2/3)

1. Cohort 2/Group 4 and Cohort 3/Group 2 Combined: To demonstrate the noninferiority of the anti–reference strain immune response after BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 30 µg compared to BNT162b2, 30 µg given as Dose 4 to BNT162b2 (Original)-experienced participants >55 years of age.
2. Cohort 2/Group 2 and Cohort 3/Group 1 combined and Cohort 2/Group 4 and Cohort 3/Group 2 combined: To describe the immune response to BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) 30 µg compared to BNT162b2, 30 µg given as Dose 4 to BNT162b2 (Original)-experienced participants 18-55 and >55 years of age.

6.1.2 Design Overview

In this ongoing study, Cohort 2 participants ≥18 years of age were randomized by age and dose level (30 µg or 60 µg) of BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine. Cohort

2 participants 12-17 years of age and Cohort 3 participants received 30 µg of BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) after having received three doses of BNT162b2, with the most recent dose from 150 to 365 days prior to randomization. The study was initiated on 26 July 2022 and the analyses presented in this report are based on a database cutoff date of 12 October 2022 (Cohort 2) and 31 October 2022 (Cohort 3). Please refer to Table 3 below.

Table 3. Evaluable Immunogenicity Population, Study C4591044, Cohort 2 and Cohort 3

Cohort/ Group	Participant Age Group (years)	Prior Doses of BNT162b2	Time since last dose (days)	Study Dose	Number of Participants
Cohort 2	-	-	-	-	-
Group 1	12-17	3	150-365	30 µg	105
Group 2	18-55	3	150-365	30 µg	95
Group 3	18-55	3	150-365	60 µg	102
Group 4	>55	3	150-365	30 µg	102
Group 5	>55	3	150-365	60 µg	99
Cohort 3	-	-	-	-	-
Group 1	18-55	3	150-365	30 µg	202
Group 2	>55	3	150-365	30 µg	184

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-protocol pg17 and c4591044-interim-c2-c3-mth1-report-body.pdf, Table 10.

Cohort 2/Group 1 and Cohort 3 were open label studies, while Cohort 2/Groups 2–5 were randomized 1:1 and observer blinded, meaning that study site personnel were blinded to the study intervention. All participants received study vaccine on Day 1 (D01) of the study.

6.1.3 Population

Summarized Inclusion Criteria: individuals ≥12 years of age who received 3 prior doses of BNT162b2, 30 µg, with the last dose being 150 to 365 days before Visit 1 (Day 1).

Summarized Exclusion Criteria: medical or psychiatric condition including recent (within past year) or active suicidal ideation/behavior, immunocompromised condition or suspected immunodeficiency, pregnant or breastfeeding. Individuals were also excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention, current or prior immunosuppressant medications, blood products, immunoglobin or monoclonal antibodies within 60 days of enrollment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) (BioNTech)

- Dose 3: 30 µg [15 µg Original, 15µg Omicron BA4/BA.5] or 60 µg [30 µg of each component], depending on the cohort. Administered as a single, intramuscular (IM) injection. Lot # 22-DP-01216 (BioNTech), PA2843276/P232708-0003L (Pfizer), PA2843276/P232708-0004L (Pfizer).

6.1.5 Directions for Use

Detailed instructions for vaccine preparation and administration are described in the full prescribing information in the Comirnaty package insert (PI).

6.1.6 Sites and Centers

Thirty U.S. clinical study sites.

6.1.7 Surveillance/Monitoring

Safety Monitoring

- Immediate AEs during 30 minutes post-Dose 3 vaccination
- Solicited AEs during 7 days post-Dose 3 vaccination. Local (IS): pain, redness, swelling. Systemic: vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, myalgia, arthralgia. Graded intensity as 1, 2, or 3. Documented by subject, or parent/guardian daily on an eDiary, and transcribed by study personnel in the case report form (CRF) at the D30 Visit.
- Unsolicited AEs to 30 days post-Dose 3 vaccination: collected by staff at each study visit and documented by investigator on CRF.
- SAEs through 6 months post-Dose 3 vaccination: defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic. The investigator assessed the causality to the investigational vaccine as either related or not related. Collected by staff at each study visit.
- Adverse Events of Special Interests (AESIs) through 6 months post-Dose 3 vaccination: Defined as confirmed diagnosis of myocarditis or pericarditis occurring within four weeks of vaccination. Reported as AE or SAE as per above procedures.

Immunogenicity (Laboratory Assays)

Blood samples were taken at Days 1 and Day 30 for immunogenicity assessments.

- SARS-CoV-2 neutralizing titers on a 384-well assay platform for reference strain (USA-WA1/2020), Omicron BA.1 and Omicron BA.4/BA.5. Conducted at Pfizer Vaccine Research and Development, Pearl River, NY. The assay was used to measure immune responses for the primary and secondary endpoints.
- SARS-CoV-2 FFRNT-NT50: Non-validated fluorescent focus reduction neutralization test (FFRNT). Conducted at University of Texas Medical Branch, Galveston, TX. The assay was used to measure immune responses for exploratory endpoints.

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

See Section 6.1.1 for study objectives and statistical criteria.

Sample Size Calculations: Approximately 500 participants were planned for enrollment into Cohort 2 and 400 participants were planned for enrollment into Cohort 3. Using a historical comparator consisting of 300 participants from Study C4591031 Substudy E and assuming a 20% non-evaluable rate, 480 evaluable participants were planned for the immunogenicity evaluations.

Immunogenicity Analyses: For the combined Cohort 2/3 analyses, the primary and secondary objectives were evaluated sequentially using a one-sided alpha of 0.025. The primary and secondary objectives in the >55 years of age group were evaluated first, followed by the primary objective for the 18-55 years of age group. Both hypotheses within the primary objectives were required to have been met prior to evaluating the next objective. Missing serology data were not imputed.

Safety Analyses: Partially missing reactogenicity data were imputed to be negative for AEs or reactions on those days. Missing AE start dates were also imputed per pre-specified safety rules. Completely missing safety data were not imputed.

6.1.10 Study Population and Disposition

Study Period: July 26, 2022, to October 12, 2022, (Cohort 2) and October 31, 2022 (Cohort 3). Data from a total of 940 participants were presented (Cohort 2, n=530; combined Cohort 2/3, n=620). Data from 210 participants (Cohort 2/Groups 2 and 4) were shared between the Cohort 2 and combined Cohort 2/3 datasets.

6.1.10.1 Populations Enrolled/Analyzed

- Randomized: participants who were assigned a randomization number in the interactive response technology (IRT) system.
- Evaluable immunogenicity: eligible, randomized participants who received the study intervention to which they are randomized/assigned, had at least one valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and had no other important protocol deviations (PD) as determined by the clinician. Analyses of the primary and secondary endpoints were based on the evaluable immunogenicity population.
- Safety population: participants who received the study intervention.

6.1.10.1.1 Demographics

Baseline demographics for Cohorts 2 and 3 are presented in Table 4 and Table 5, respectively. The time since the last dose of BNT162b2 was an average of 8-10 months prior to study vaccination in Cohort 2, and 10-11 months prior to study vaccination in the combined Cohort 2/3. The percentage of participants who were obese ranged from 6.8% to 40.0% of participants in Cohort 2 and was 39.7% of the combined Cohort 2/3 participants.

Table 4. Demographic Characteristics, Safety Population, Cohort 2, Study C4591044

Demographics	Group 1 12-17 YOA 30 µg[a] N=107 n (%)	Group 2 18-55 YOA 30 µg[a] N=103 n (%)	Group 3 18-55 YOA 60 µg[a] N=110 n (%)	Group 4 >55 YOA 30 µg[a] N=106 n (%)	Group 5 >55 YOA 60 µg[a] N=102 n (%)
Sex	-	-	-	-	-
Male	59 (55.1)	44 (42.7)	47 (42.7)	65 (61.3)	47 (46.1)
Female	48 (44.9)	59 (57.3)	63 (57.3)	41 (38.7)	55 (53.9)
Race	-	-	-	-	-
White	91 (85.0)	82 (79.6)	90 (81.8)	84 (79.2)	92 (90.2)
Black or African American	9 (8.4)	9 (8.7)	11 (10.0)	16 (15.1)	8 (7.8)
American Indian or Alaska Native	0	0	0	1 (0.9)	0
Asian	3 (2.8)	10 (9.7)	9 (8.2)	3 (2.8)	2 (2.0)
Native Hawaiian or Pacific Islander	0	0	0	1 (0.9)	0
Multiracial	3 (2.8)	2 (1.9)	0	1 (0.9)	0
Ethnicity	-	-	-	-	-
Hispanic/Latino	7 (6.5)	12 (11.7)	15 (13.6)	10 (9.4)	11 (10.8)
Not Hispanic/Latino	98 (91.6)	90 (87.4)	94 (85.5)	96 (85.5)	88 (86.3)

Demographics	Group 1 12-17 YOA 30 µg[a] N=107 n (%)	Group 2 18-55 YOA 30 µg[a] N=103 n (%)	Group 3 18-55 YOA 60 µg[a] N=110 n (%)	Group 4 >55 YOA 30 µg[a] N=106 n (%)	Group 5 >55 YOA 60 µg[a] N=102 n (%)
Mean Age (Min, Max)	15.1 (12, 17)	39.6 (19, 55)	40.0 (18, 55)	65.7 (56, 79)	63.8 (56, 85)
Baseline Positive SARS-CoV-2 N (%)	81 (75.7)	66 (64.1)	82 (74.5)	64 (60.4)	67 (65.7)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 14
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine.
N, total number of participants in a specific group; n (%), number and percentage of participants
Positive SARS-CoV-2 status was defined as positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
Abbreviations: YOA, years of age

Table 5. Demographic Characteristics, Safety Population, Combined Cohort 2/3, Study C4591044

Demographics	18-55 YOA 30 µg[a] N=313 n (%)	>55 YOA 30 µg[a] N=306 n (%)
Sex	-	-
Male	112 (35.8)	139 (45.4)
Female	201 (64.2)	167 (54.6)
Race	-	-
White	251 (80.2)	243 (79.4)
Black or African American	26 (8.3)	48 (15.7)
American Indian or Alaska Native	0	3 (1.0)
Asian	32 (10.2)	8 (2.6)
Native Hawaiian or Pacific Islander	0	1 (0.3)
Multiracial	4 (1.3)	3 (1.0)
Ethnicity	-	-
Hispanic/Latino	39 (12.5)	37 (12.1)
Not Hispanic/Latino	272 (86.9)	267 (87.3)
Mean Age (Min, Max)	39.3 (18, 55)	65.6 (56, 87)
Baseline Positive SARS-CoV-2 N (%)	222 (70.9)	187 (61.1)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 15
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine.
N, total number of participants in a specific group; n (%), number and percentage of participants
Positive SARS-CoV-2 status was defined as positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
Abbreviations: YOA, years of age

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentage of study participants who were overweight or obese are described in Section 6.1.10.1.

6.1.10.1.3 Subject Disposition

The disposition of study participants from Cohort 2 and combined Cohort 2/3 are included in Table 6 and Table 7.

Table 6. Participant Disposition, Cohort 2, Study C4591044

Disposition	Group 1 12-17 YOA 30 µg[a] n (%)	Group 2 18-55 YOA 30 µg[a] n (%)	Group 3 18-55 YOA 60 µg[a] n (%)	Group 4 >55 YOA 30 µg[a] n (%)	Group 5 >55 YOA 60 µg[a] n (%)
Randomized	108 (100)	104 (100)	110 (100)	106 (100)	102 (100)
Vaccinated	108 (100)	103 (99.0)	110 (100)	106 (100)	102 (100)
Safety Population	107 (99.0)	103 (99.0)	110 (100)	106 (100)	102 (100)
Evaluable immunogenicity	105 (97.2)	95 (91.3)	102 (92.7)	102 (96.2)	99 (97.1)
Participants without evidence of SARS-CoV-2 infection up to 1 month after study vaccination[b]	25 (23.1)	32 (30.8)	23 (20.9)	40 (37.7)	31 (30.4)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 5, Table 7, Table 10
n (%), number and percentage of participants
The randomized population is used as the denominator for subsequent participant populations, except for the 1-month immunogenicity population in which 40 and 39 participants were respectively randomized into Groups 2 and 4.
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine.
b. Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Abbreviations: YOA, years of age

Table 7. Participant Disposition, Combined Cohort 2/3, Study C4591044

Disposition	18-55 YOA 30 µg[a] n (%)	>55 YOA 30 µg[a] n (%)
Randomized	314 (100)	306 (100)
Vaccinated	313 (99.7)	306 (100)
Safety Population	313 (99.7)	306 (100)
Evaluable immunogenicity	297 (94.6)	286 (93.5)
Participants without evidence of infection up to 1 month after study vaccination[b]	77 (24.5)	105 (34.3)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 6, Table 8, Table 13
n (%), number and percentage of participants
The randomized population is used as the denominator for subsequent participant populations.
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine.
Participants who had no serological or virological evidence (up to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the study vaccination, the 7-day (if available) and the 1-month post–study vaccination visits, negative NAAT [nasal swab] at the study vaccination visit, and any unscheduled visit up to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
Abbreviations: YOA, years of age

The percentages of study C4591044 Combined Cohort 2/3 participants 18-55 years of age, and >55 years of age who were SARS-CoV-2 seropositive at baseline (prior to Dose 4) were 24.5% and 34.3%, respectively.

The comparator group for the primary and secondary analyses in participants >55 years of age were 238 age-matched Study C4591031 Substudy E participants who received 30 µg BNT162b2 (Original). The median time from the last BNT162 dose to the study vaccination was approximately 6 months, and 14.2% of participants were SARS-CoV-2 baseline positive.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary and Secondary Endpoint(s)

Neutralizing GMTs, Omicron BA.4/BA.5 strain (primary endpoint) and reference strain (secondary endpoint)

In participants >55 years of age, GMRs were determined for Study C4591044 participants who received 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) as Dose 4, compared to Study C4591031 Substudy E participants who received 30 µg BNT162b2 as Dose 4 (Table 8). The criteria were met for comparisons of the ratio of neutralizing antibody GMTs after 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccination with GMTs after 30 µg BNT162b2 vaccination, defined as follows:

- Statistical superiority criterion: the LL of the 2-sided 95% CI for the GMR ($GMT_{\text{Study C4591044 30 µg BNT162b2 Bivalent}}$/ $GMT_{\text{Study C4591031 30 µg BNT162b}}$) using the Omicron BA.4/BA.5 strain was >1
- Noninferiority criteria: the LL of the 2-sided 95% CI for the GMR ($GMT_{\text{Study C4591044 30µg BNT162b2 Bivalent}}$/ $GMT_{\text{Study C4591031 30µg BNT162b}}$) using the reference strain was >0.67 and the point estimate of the GMR was ≥0.8

In Study C4591044 participants 18-55 years of age compared with participants >55 years of age who received Dose 4 of 30 µg BNT162b2 Bivalent, the noninferiority criterion was met for comparisons with 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) by age. The LL of the 2-sided 95% CI for the GMR (18-55 YOA / >55 YOA) was >0.67. The percentages of study C4591044 participants 18-55 years of age, and >55 years of age who were SARS-CoV-2 seropositive at baseline (prior to Dose 4) were 71.7% and 61.5%, respectively.

Table 8. Geometric Mean Ratios, Participants With or Without Evidence Of SARS-CoV-2 Infection at 1 Month Post-Dose 4, Evaluable Immunogenicity Population, Study C4591044 Combined Cohort 2/3, and Study C4591031 Substudy E

SARS-CoV-2 Variant	Bivalent BNT162b[a] 18-55 YOA n=297 GMT (95% CI)	Bivalent BNT162b2[a] >55 YOA n=282-284 GMT (95% CI)	BNT162b2[b] >55 YOA n=273-287 GMT (95% CI)	[Vaccine Comparison] >55 YOA Bivalent BNT162b2[a] / BNT162b2[b] GMR (95% CI)	[Age Group Comparison] Bivalent BNT162b2[a] 18-55 YOA / >55 YOA GMR (95% CI)
Omicron BA.4/BA.5 - NT50 (titer)	4455.9 (3851.7, 5154.8)	4158.1 (3554.8, 4863.8)	938.9 (802.3, 1098.8)	2.91 (2.45, 3.44)[c]	0.98 (0.83, 1.16)[d]
Reference strain – NT50 (titer)	-	16250.1 (14499.2, 18212.4)	10415.5 (9366.7, 11581.8)	1.38 (1.22, 1.56)[e]	-

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 37 and Table 14.32
SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (reference strain [USA-WA1/2020], Omicron B.1.1.529 subvariant BA.4/BA.5).
n = Number of participants with valid and determinate assay results for the specified assay at the given sampling timepoint.
Evaluable population: participants enrolled in each age group (18-55 years, >55 years) in Study C4591044 30µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) Cohort 2&3 groups combined and all participants >55 years of age from Study C4591031 Substudy E 30µg BNT162b2 group who met evaluability criteria
a. 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) administered in study C4591044 Cohort 2 and 3 combined
b. 30 µg BNT162b2 (Original) administered in study C4591031 substudy E
c. Statistical superiority was declared if the LL of the 2-sided 95% CI for the GMR was >1.
d. Noninferiority was declared if the LL of the 2-sided 95% CI for the GMR was >0.67.
e. Noninferiority was declared if the LL of the 2-sided 95% CI for the GMR was >0.67 and the point estimate of the GMR was ≥0.8.
GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distr bution). Assay results below the LLOQ were set to 0.5 × LLOQ.
Model-based GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on a regression model
Abbreviations: YOA, years of age; GMR, geometric mean ratio; LL, lower limit; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Reviewer Comment:
In participants who were baseline (pre-booster) SARS-CoV-2 positive, GMTs for both Omicron B.1.1.529 subvariant BA.4/BA.5) and USA-WA1/2020 reference strains were higher compared to participants who were baseline SARS-CoV-2 negative [18-55 YOA: baseline positive, Post-Dose 4: GMT 6040 vs. baseline negative, Post-Dose 4: GMT 2045; >55 YOA: baseline positive, Post-Dose 4: GMT 6755 vs. baseline negative, Post-Dose 4: GMT 1914], supporting that hybrid immunity (i.e., prior SARS-CoV-2 infection then single vaccination) may improve immune response.

Seroresponse rates, Omicron BA.4/BA.5 strain (primary endpoint)
In participants >55 years of age, seroresponse rates were determined for Study C4591044 participants who received 30 µg BNT162b2 Bivalent, (Original and Omicron BA.4/BA.5) as Dose 4, compared with Study C4591031 Substudy E participants who received 30 µg BNT162b2 as Dose 4 (Table 9, Vaccine Comparison). The noninferiority criterion was met for comparison of percentage of seroresponse rate, using the Omicron BA.4/BA.5 strain; the LL of the 2-sided 95% CI for the difference in percentage of participants with seroresponse (study C4591044 30µg BNT162b2 Bivalent minus Study C4591031 30 µg BNT162b) was >-10%.

The percentage difference in seroresponse was also compared between study C4591044 participants 18-55 years of age and participants >55 years of age who received 30 µg BNT162b2 Bivalent, Dose 4 (Table 9, Age Group Comparison). The noninferiority criterion was

met for comparison with 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) seroresponse, by age. The LL of the 2-sided 95% CI of the difference in the percentage of participants with seroresponse (18-55 years of age minus >55 years of age) was >-5%.

Table 9. Percentage Difference in Seroresponse Rate Among Participants With or Without Evidence Of SARS-CoV-2 Infection at 1 Month Post-Dose 4 Vaccination, Evaluable Immunogenicity Population, Study C4591044 Combined Cohort 2/3, and Study C4591031 Substudy E

SARS-CoV-2 Variant	Bivalent BNT162b[a] 18-55 YOA N=294 % (n) (95% CI)	Bivalent BNT162b[a] >55 YOA N=282 % (n) (95% CI)	BNT162b2[b] >55 YOA N=273 % (n) (95% CI)	[Vaccine Comparison] >55 YOA SRR% Difference[c] Bivalent BNT162b2[a] minus BNT162b2[b] (95% CI)[d]	[Age Group Comparison] SRR% Difference[c] Bivalent BNT162b2[a] 18-55 YOA minus >55 YOA (95% CI)[d]
Omicron BA.4/BA.5 - NT50 (titer)	61.2 (180) (55.4, 66.8)	66.7 (188) (60.8, 72.1)	46.5 (127) (40.5, 52.6)	-3.03 (-9.68, 3.63)[e]	26.77 (19.59, 33.95)[f]

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 39
SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron B.1.1.529 subvariant BA.4/BA.5).
N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation. n = Number of participants with seroresponse for the given assay at the given sampling time point.
a. 30µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) administered in study C4591044 Cohort 2 and 3 combined
b. 30µg BNT162b2 (Original) administered in study C4591031 substudy E
c. Difference in percentage of participants with ≥4-fold rise from pre-booster [pre-dose 4] to post-booster [post-Dose 4], expressed as a percentage.
d. 2-Sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (<median, ≥ median) for the difference in proportions. The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
e. Noninferiority was declared if the LL of the 2-sided 95% CI for the difference in seroresponse rate was >-10%.
f. Noninferiority was declared if the LL of the 2-sided 95% CI for the difference in seroresponse rate was >-5%.
Seroresponse was defined a ≥4-fold increase in post-booster vaccination titer from baseline (before the study vaccination). If the baseline titer was <LLOQ, a post-booster vaccination titer ≥4 × LLOQ was considered a seroresponse.
Abbreviations: LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Neutralizing GMTs and Seroresponse, 12-17 years of age (descriptive endpoint)

Immune responses after 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) booster vaccination in Study C4591044 Cohort 2/Group 1 (12-17 years of age) compared to Cohorts 2 and 3 (18-55, >55 years of age) are described in Table 10.

Table 10. Geometric Mean Titers at 1 Month After 30 µg Bivalent BNT162b (Original and Omicron BA.4/BA.5) Dose 4, Participants With or Without Evidence of Infection, Evaluable Immunogenicity, Study C4591044

SARS-CoV-2 Variant	12-17 YOA 30 µg Bivalent BNT162b[a] n= 104-105 GMT (95 CI%)	18-55 YOA 30 µg Bivalent BNT162b[a] n= 294-297 GMT (95 CI%)	>55 YOA 30 µg Bivalent BNT162b[a] n= 284-286 GMT (95 CI%)
Omicron BA.4/BA.5	-	-	-
Pre-booster	1105.8 (835.1, 1464.3)	569.6 (471.4, 688.2)	458.2 (365.2, 574.8)
One-month post-booster	8212.8 (6807.3, 9908.7)	4455.9 (3851.7, 5154.8)	4158.1 (3554.8, 4863.8)

SARS-CoV-2 Variant	12-17 YOA 30 µg Bivalent BNT162b[a] n= 104-105 GMT (95 CI%)	18-55 YOA 30 µg Bivalent BNT162b[a] n= 294-297 GMT (95 CI%)	>55 YOA 30 µg Bivalent BNT162b[a] n= 284-286 GMT (95 CI%)
Reference strain	-	-	-
Pre-booster	6863.3 (5587.8, 8430.1)	4017.3 (3430.7, 4704.1)	3690.6 (3082.2, 4419.0)
One-month post-booster	23641.3 (20473.1, 27299.8)	16323.3 (14686.5, 18142.6)	16250.1 (14499.2, 18212.4)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 14.20 and 14.32
SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
a. 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) administered in study C4591044, Cohort 2/Group 1 (12-17 YOA), Cohort 2&3 combined (18-55 YOA, >55 YOA)
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t-distribution). For purposes of GMT calculations, titers < than the LLOQ were set to 0.5 × LLOQ.
Abbreviations: LLOQ, lower limit of quantitation; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; YOA, years of age

As shown in Table 10, GMTs one month after vaccination were higher than pre-vaccination GMTs. Participants 12-17 years of age had the highest GMTs, with participants 18-55 years of age and >55 years of age having similar responses per dose. In participants who were baseline (pre-booster) SARS-CoV-2 positive, seroresponse rates for both strains were higher compared to participants who were baseline SARS-CoV-2 negative (data not shown).

Table 11. Seroresponse Rates, at 1 Month After 30 µg Bivalent BNT162b (Original and Omicron BA.4/BA.5) Dose 4, Participants With or Without Evidence of Infection, Evaluable Immunogenicity, Study C4591044

SARS-CoV-2 Variant	12-17 YOA 30 µg Bivalent BNT162b[a] N=104 % (n) (95% CI)	18-55 YOA 30 µg Bivalent BNT162b[a] N=294-295 % (n) (95% CI)	>55 YOA 30 µg Bivalent BNT162b[a] N=282-284 % (n) (95% CI)
Omicron BA.4/BA.5	66.3 (69) (56.4, 75.3)	61.2 (180) (55.4, 66.8)	66.7 (188) (60.8, 72.1)
Reference strain	41.0 (43) (31.5, 51.0)	44.1 (130) (38.3, 49.9)	45.8 (130) (39.9, 51.8)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 14.24 and Table 45
SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
a. 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) administered in study C4591044, Cohort 2/Group 1 (12-17 YOA), Cohort 2&3 combined (18-55 YOA, >55 YOA)
Seroresponse was defined a ≥4-fold increase in post-booster vaccination titer from baseline (before the study vaccination). If the baseline titer was <LLOQ, a post-booster vaccination titer ≥4 × LLOQ was considered a seroresponse.
Abbreviations: NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, YOA, years of age

For both strains, seroresponse rates in participants 12-17 years of age were similar to seroresponse rates in adults >18 YOA. For all age groups, seroresponse rates to the reference strain were generally lower than rates observed to the Omicron BA.4/BA.5 strain.

6.1.11.3 Subpopulation Analyses

Immunogenicity results were generally similar between male and female participants. No subgroup analysis by race or ethnicity was provided in this interim report.

6.1.11.5 Exploratory and Post Hoc Analyses

Other variants were evaluated using FFRNT assays, which are unvalidated. A numerical increase in GMTs and seroresponse rates were observed for Omicron BA.4.6, Omicron BA.2.75.2, Omicron BQ 1.1 and Omicron XBB at one month after vaccination. The numerical increase was greater for combined Cohort 2/3 participants >55 years of age (vaccinated with 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) compared to participants >55 years of age who were enrolled in Study C4591031 Substudy E (vaccinated with 30 µg BNT162b).

6.1.12 Safety Analyses

6.1.12.1 Methods

See section 6.1.7.

6.1.12.2 Overview of Adverse Events

The safety data were presented for each group in Cohort 2 and the combined Cohort 2/3 study groups population. The median time of safety follow-up was 1.5 months up to a data cutoff date of October 31, 2022. Table 12 below provides data for each group by type of adverse events.

Table 12. Summary of Adverse Events, Participants with at Least 1 Adverse Event from the Study Vaccination Through 1 Month after the Study Vaccination, Safety Population, Cohort 2/Group1-5 and Combined Cohort 2/3, Study C4591044

AE Type: Monitoring Period	Cohort 2 12-17 YOA 30 µg[a] N=107 n (%)	Cohort 2 18-55 YOA 60 µg[a] N=110 n (%)	Cohort 2 >55 YOA 60 µg[a] N=101-102 n (%)	Combined Cohort 2/3 18-55 YOA 30 µg[a] N=309-313 n (%)	Combined Cohort 2/3 >55 YOA 30 µg[a] N=300-306 n (%)
Immediate AE: 30 minutes	1 (0.9)	0 (0)	0 (0)	1 (0.3)	0 (0)
Solicited Local: 7 days	75 (70.1)	103 (93.6)	73 (71.6)	240 (77.4)	174 (57.8)
Solicited Systemic: 7 days	86 (80.4)	90 (81.8)	64 (63.4)	229 (74.1)	162 (53.8)
Unsolicited AE: 30 days	8 (7.5)	9 (8.2)	7 (6.9)	19 (6.1)	21 (6.9)
AEs leading to withdraw: 30 days	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs: 30 days	0 (0)	0 (0)	0 (0)	1 (0.3)	2 (0.7)
Deaths: 30 days	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 14.41, Table 14.48, Table 47, Table 14.69
N = Number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination. n = number of participants with the specified adverse reaction.
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)

Study participants within the same age group who received BNT162b2 Bivalent (Original and Omicron BA.4/BA.5), participants in the 60 µg groups had higher rates of solicited local and systemic reactions than those who received 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5). Rates of solicited local and systemic reactions were similar across age groups who received the same dose level of vaccine. Subgroup analyses by sex and baseline SARS-CoV-2 status did not identify any differences in rates of solicited reactions.

Table 13. Solicited Reactions, Safety Population, Cohort 2/Groups1-5 and Combined Cohort2/3, Study C4591044

Solicited Adverse Reaction	Cohort 2 12-17 YOA 30 µg[a] N=107 n (%)	Cohort 2 18-55 YOA 60 µg[a] N=110 n (%)	Cohort 2 >55 YOA 60 µg[a] N=101 n (%)	Combined Cohort 2/3 18-55 YOA 30 µg[a] N=309-310 n (%)	Combined Cohort 2/3 >55 YOA 30 µg[a] N=300-301 n (%)
Local (Injection site) Reactions	-	-	-	-	-
Redness	-	-	-	-	-
Any	6 (5.6)	12 (10.9)	7 (6.9)	21 (6.8)	11 (3.7)
Severe	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)
Pain	-	-	-	-	-
Any	75 (70.1)	103 (93.6)	72 (70.6)	236 (76.1)	172 (57.1)
Severe	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (0.3)
Swelling	-	-	-	-	-
Any	8 (7.5)	17 (15.5)	9 (8.9)	23 (7.4)	8 (2.7)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Systemic Reactions	-	-	-	-	-
Fever	-	-	-	-	-
Any	10 (9.3)	13 (11.8)	14 (13.9)	15 (4.9)	14 (4.7)
>40.0°C	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	-	-	-	-	-
Any	72 (67.3)	76 (69.1)	54 (53.5)	189 (61.2)	116 (38.5)
Severe	0 (0)	1 (0.9)	4 (4.0)	6 (1.9)	4 (1.3)
Headache	-	-	-	-	-
Any	54 (50.5)	50 (45.5)	36 (35.6)	144 (46.6)	92 (30.7)
Severe	0 (0)	1 (0.9)	1 (1.0)	2 (0.6)	0 (0)
Chills	-	-	-	-	-
Any	25 (23.4)	30 (27.3)	23 (22.8)	68 (22.0)	36 (12.0)
Severe	0 (0)	1 (0.9)	0 (0)	2 (0.6)	1 (0.3)
Vomiting	-	-	-	-	-
Any	3 (2.8)	2 (1.8)	3 (3.0)	6 (1.9)	2 (0.7)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	-	-	-	-	-
Any	7 (6.5)	14 (12.7)	7 (6.9)	33 (10.7)	29 (9.6)
Severe	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)
Myalgia	-	-	-	-	-
Any	28 (26.2)	46 (41.8)	23 (22.8)	94 (30.4)	54 (18.0)
Severe	0 (0)	1 (0.9)	1 (1.0)	0 (0)	0 (0)
Arthralgia	-	-	-	-	-
Any	13 (12.1)	27 (24.5)	15 (14.9)	46 (14.9)	36 (12.0)
Severe	0 (0)	1 (0.9)	1 (1.0)	0 (0)	0 (0)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 14.41, Table 14.48, Table 14.69, Table 14.76

BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)

N = Number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination. N = 310 for redness and pain at injection site in participants 18-55 years of age; N=301 for pain at injection site in participants >55 years of age. N=301 for fever, headache, fatigue and diarrhea. n = number of participants with the specified adverse reaction.

Severe solicited local reactions: redness, swelling: >10.0 cm, pain at the injection site: prevents daily activity.

Severe solicited systemic reactions: fatigue, headache, chills, myalgia, arthralgia: prevents daily activity; vomiting: requires intravenous hydration; diarrhea: 6 or more loose stools in 24 hours.

Solicited Adverse Reactions:
Table 13 includes the number and percentage of any solicited reaction and Severe/Grade 4 solicited reactions in Cohort 2/Groups 1-5 and combined Cohorts 2/3 study participants. For all groups, IS pain was the most common adverse reaction following vaccination. Fatigue was the most common solicited systemic reaction across all groups. Most adverse reactions and adverse events were determined to be mild or moderate in severity, with a minority of events determined to be severe or Grade 4 severity. Most solicited reactions occurred in the first 1-2 days after vaccination and lasted 1-2 days.

Immediate AEs:
Two study participants experienced an adverse event within thirty minutes of vaccination administration. One study participant in the 12-17 years of age group in Cohort 2 experienced Grade 2 IS erythema, described as a "5cm circular oval erythematous" area at the IS that resolved in one day. The second study participant was enrolled in the Combined 2/3 Cohorts in the 18-55 years of age group and experienced Grade 1 IS erythema, pain and swelling that resolved within 2-3 days.

Unsolicited Adverse Events:
At least one unsolicited adverse event within a month of vaccination was reported by 31 participants in all age groups in Cohort 2, and 40 participants in the combined Cohort 2/3. The most common unsolicited adverse events were within the *Musculoskeletal and Connective tissue disorders* category (n=12) with *Myalgias* and *Arthralgias* as the most common adverse events reported. Study participants >55 years of age who received 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5), reported the most AEs in this category (n=5, 2.6%).

Blood and lymphatic system disorders (n=9) and Injury, poisoning and procedural complications (n=9) were the other common categories of AEs. The most common AE within *Blood and Lymphatic system disorders* was *Lymphadenopathy* (n=7). Study participants 18-55 years of age who received 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5), reported the most AEs in this category (n=4, 2%). AEs in the *Injury, Poisoning and Procedural complications* were sporadic, and the most common AE was falls in individuals >55 years of age.

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Three serious adverse events were observed within a month of vaccination in Cohort 2 and the Combined Cohort 2/3 datasets. None of the SAEs were considered by the study investigator or FDA to be related to the study vaccine.

- 54-year-old female (Cohort 3, 30 µg, BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) developed hypotension nine days after study vaccination, after experiencing an episode of vomiting in association with concomitant medication for hypertension. The event lasted one day and resolved at the time of the interim study report.
- 79-year-old male (Cohort 2, 30 µg, BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) developed dyspnea needing hospitalization 15 days after study vaccination. The event was reported as ongoing at the time of the interim study report.
- 74-year-old female (Cohort 3, 30 µg, BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) developed hyperglycemia associated with worsening of Type 2 Diabetes 15 days after study vaccination and was hospitalized. The event lasted 14 days and was resolved at the time of the interim study report.

6.1.12.5 Adverse Events of Special Interest

No myocarditis or pericarditis were reported within a month of study vaccination.
Lymphadenopathy: described in the unsolicited AE section.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

Across study groups, 521 (98.3%) participants in Cohort 2 completed the 1-month study visit and 609 (98.2%) participants completed the 1-month study visit in Combined Cohort 2/3. There were no discontinuations due to an AE.

Table 14. Participant Disposition, Cohort 2, and Combined Cohort 2/3, Study C4591044

Disposition	Cohort 2 12-17 YOA 30 µg[a] n (%)	Cohort 2 18-55 YOA 60 µg[a] n (%)	Cohort 2 >55 YOA 60 µg[a] n (%)	Combined Cohort 2/3 18-55 YOA 30 µg[a] n (%)	Combined Cohort 2/3 >55 YOA 30 µg[a] n (%)
Randomized: N (%)	108 (100)	110 (100)	102 (100)	314 (100)	306 (100)
Vaccinated	108 (100)	110 (100)	102 (100)	313 (99.7)	306 (100)
Completed 1-month visit	108 (100)	106 (96.4)	101 (99.0)	307 (97.8)	302 (98.7)
Did not complete trial:	-	-	-	-	-
Withdrawal	0 (0)	1 (0.9)	0 (0)	2 (0.6)	0 (0)
Lost to follow-up	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)

Source: Adapted from IND19736/1053, c4591044-interim-c2-c3-mth1-report-body.pdf, Table 5, Table 6
a. BNT162b2 Bivalent (Original and Omicron BA.4/BA.5)
Abbreviations: YOA, years of age, N, total number of participants; n (%), number and percentage of participants in group

Four study participants discontinued the study. One withdrew consent and did not receive study vaccine. This participant was also excluded from the safety population. One participant withdrew themselves and a second participant was withdrawn by their physician as they could not be available for follow-up visits.

6.1.13 Study Summary and Conclusions

Study C4591044 was designed to be a randomized active-controlled Phase 2/3 study that evaluates the safety and immunogenicity in the population with or without evidence of SARS-CoV-2 infection up to 1-month postvaccination of BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) vaccine administered Dose 4 in individuals ≥12 years of age.

- For participants >55 YOA, evaluations of SARS-CoV-2 GMTs and seroresponse rates against the B.1.1.529 (Omicron BA.4/BA.5) and USA_WA1/2020 reference strains elicited by 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) (study 1044) were compared with responses after 30 ug BNT162b2 (Original) (age-matched participants from study 1031 substudy E). The statistical criteria for the primary objectives in participants >55 YOA were met as the geometric mean ratio (GMR; Bivalent BA.4/BA.5 divided by BNT162b2) of neutralizing antibody titers against Omicron BA.4/BA.5 was 2.91 (LL of 95% CI: 2.45), demonstrating statistical superiority based on a lower bound of the 95% CI >1.0, and the percentage seroresponse rate difference (Bivalent BA.4/BA.5 minus BNT162b2) evaluating seroresponse from pre-study intervention to 1-month postvaccination against Omicron BA.4/BA.5 was -3.03% (LL of 95% CI: -9.68%), demonstrating statistical

noninferiority based on a lower bound of the 95% CI >−5%; the criteria for the secondary endpoint was also met as the GMR against the reference strain was 1.38 (LL of 95%CI: 1.22), demonstrating statistical noninferiority based on a lower bound of the 95% CI >0.67 and a point estimate ≥0.8.

- For participants 18-55 years of age (study 1044 18-55 years of age vs. study 1044 >55 years of age), the primary endpoints were met, based on noninferiority comparisons of the GMR and percentage difference in seroresponse rates using the USA_WA1/2020 reference strain.

The statistical criteria for the primary and secondary endpoints, as described above, demonstrate immunobridging of the BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) to the BNT162b2 (Original) regimen whose clinical efficacy has been demonstrated, and therefore supported the statutory standard of substantial evidence for the approval of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older. See Appendix B for the Applicant's case definition of COVID-19 infection. Also, subgroup analyses indicated neutralizing antibody GMTs in participants who were previously vaccinated with BNT162b2 (Original) and had evidence of prior SARS-CoV-2 infection (i.e., a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity) were higher than GMTs in BNT162b2 (Original)-experienced participants (vaccine only) without evidence of prior SARS-CoV-2 exposure. The safety of 30 µg BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) was similar to the safety profile of 30 µg BNT162b2 (Original).

6.2 Study C4591031

NCT04955626
"A Phase 3 Master Protocol To Evaluate Additional Dose(S) Of BNT162b2 In Healthy Individuals Previously Vaccinated With BNT162b2."

Study Overview
Study C4591031 safety data (SAEs, AESIs) from Substudies A and C provided supportive safety and immunogenicity data up to 1-month of a single dose use (a third dose) of COMIRNATY, including Comirnaty (2023-2024 Formula), in individuals ≥12 years of age who were previously vaccinated with a 2-dose regimen of COVID-19 vaccine prior to randomization. Study C4591031 was designed to evaluate BNT162b2 boosting strategies in healthy individuals who were previously vaccinated with BNT162b2 (Original). From the six substudies, only the safety data from Substudy A (16-55 years of age) and Substudy C (12-17 years of age) are presented in this memo following BNT162b2 (Original) Dose 3.

The interim report for Substudy A (version 2.0 dated June 7, 2022,) contains 6-month safety data from participants 16-55 years of age who received 30 µg BNT162b2 (Original) Dose 3 after completing two doses of BNT162b2 (Original). Enrollment started July 1, 2021, and the interim data cutoff date was February 8, 2022.

The interim report for Substudy C (version 1.0 dated December 8, 2022) contains 1-month safety data from participants 12-17 years of age who received 30 µg BNT162b2 (Original) Dose 3 after completing two doses of BNT162b2 (Original). Enrollment started December 20, 2021, and the interim data cutoff date was July 14, 2022.

6.2.1 Objectives

The safety objectives were:

Substudy A: To describe the safety and tolerability profile of 30 µg BNT162b2 (Original), given as a Dose 3 to BNT162b2 (Original)-experienced participants.

Reviewer Comment*: In this substudy, solicited local reactions or systemic AEs were not assessed.*

Substudy C: To evaluate the safety of BNT162b2 (Original) Dose 3 when administered at dose levels of 10 µg and 30 µg.

For both Substudies, the endpoints relevant to this sBLA safety review were:

- SAEs from administration of study vaccination through 6 months postvaccination
- AESIs from administration of study vaccination through 6 months postvaccination

This study provided the largest number of a 30 µg BNT162b2 (Original) Dose 3 recipients ≥16 years of age with at least 6 months of follow-up (N=5025).

6.2.2 Design Overview

Substudy A: randomized, placebo-controlled, observer-blind substudy to evaluate the safety, tolerability, and efficacy of BNT162b2 (Original) Dose 3. Participants ≥16 years of age who completed two doses of BNT162b2 (Original) at least 6 months (175 days) prior to randomization were randomized at a ratio of 1:1 to receive either BNT162b2 (Original) or placebo. Randomization was stratified by age, such that approximately 60% of participants enrolled were ≥16-55 years of age and approximately 40% of participants >55 years of age. Planned enrollment was 10,000.

Substudy C: randomized, observer-blinded substudy to evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Original) Dose 3 at 10 µg and at 30 µg. Participants ≥12 years of age who completed two doses of 30 µg BNT162b2 (Original), at least 5 months (150 days) prior to randomization were enrolled. Participants were randomized at a ratio of 1:1 to receive BNT162b2 (Original) at a dose level of either 10 µg or 30 µg. Up to approximately 150 participants were randomized in the 12-17 years of age group in this study. However, during the course of the study, the ACIP recommended a third dose of COVID-19 vaccine, administered as a Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), for all age groups. Since the 30 µg dose level was well tolerated in individuals 12-17 years of age, and in the face of emergence of SARS-CoV-2 Omicron sublineages for which a maximum immune response was desirable, evaluation of a reduced dose of BNT162b2 (Original), 10 µg was discontinued.

Safety assessments included reactogenicity (prompted local reactions and systemic events) collected in an e-diary for 7 days after Dose 3 and unsolicited AEs reported during follow-up through a data cutoff date of July 14, 2022. Safety follow-up of enrolled participants continued through 6 months after the study vaccination.

6.2.3 Population

Evidence of SARS-CoV-2 infection at baseline was determined by serological testing (N-binding assay) result at Dose 3 visit or medical history of COVID-19.

Substudy A
Summarized Inclusion Criteria: participants ≥16 years of age who had received 2 doses of BNT162b2 30 µg, 19-42 days apart during Study C4591001, with Dose 2 being at least 175 days before Visit 1 (Day 1) in Study C4591031.

Summarized Exclusion Criteria: previous diagnosis of COVID-19, immunocompromised condition or suspected immunodeficiency, pregnant or breastfeeding, history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention, current or prior receipt of immunosuppressant medications, recent receipt of blood products, recent receipt of immunoglobin or monoclonal antibodies within 60 days of enrollment, or previously received a COVID-19 vaccine other than BNT162b2 (Original).

Substudy C
Summarized Inclusion Criteria: Participants ≥12 years of age who had received 2 doses of BNT162b2 (Original) 30 µg,19-60 days apart during Study C4591001, with Dose 2 being at least 150 days before Visit 1 (Day 1) of Study C4591031.

Summarized Exclusion Criteria: same as for substudy A.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Substudies A and C
Study Intervention: BNT162b2 (Original) (BNT162 RNA-LNP vaccine utilizing modRNA)
Unit Dose Strength(s): 250 µg/0.5 mL
Dosage Level(s) 30 µg (Substudy A and Substudy C); 10 µg (Substudy C only)
Route of Administration: IM injection

6.2.5 Directions for Use

Substudies A and C
Detailed instructions for preparing BNT162b2 are described in the full prescribing information in the COMIRNATY PI.

6.2.6 Sites and Centers

Substudy A was conducted at 123 sites: U.S. (117), South Africa (4), and Brazil (2).
Substudy C was conducted at 47 sites: Germany (3), South Africa (3), and United States (41).

6.2.7 Surveillance/Monitoring

Substudies A and C
An independent Data Monitoring Committee (DMC) reviewed safety data routinely and on an ad hoc basis.

Safety monitoring pertinent to this sBLA review:
Immediate AEs: defined as any AE reported within 30 minutes post-Dose 3 vaccination.

- Unsolicited AE: assessed through 1-month post-Dose 3 vaccination. Defined as an untoward medical occurrence, such as abnormal laboratory results, exacerbation of a chronic or intermittent preexisting condition, new condition, suspected drug-drug interaction or suspected drug overdose that occurs within 1 month of study vaccination. AEs were graded based on intensity of interference in usual function: 1 – mild (no interference), 2 – moderate (some interference), 3 – severe (significant interference), or 4 – life-threatening (major interference requiring urgent intervention).

- SAE: assessed through 6 months post-Dose 3 vaccination. Defined as an untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in a persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect.
- AESI: assessed through 6 months post-Dose 3 vaccination. Defined as a confirmed diagnosis of myocarditis or pericarditis (i.e., clinical signs/symptoms and positive SARS-CoV-2 NAAT test) occurring within four weeks of vaccination. Reported as AE or SAE, depending on if the event was non-serious or serious.

6.2.8 Endpoints

Substudies A and C: See Section 6.2.1

6.2.9 Statistical Considerations & Statistical Analysis Plan

Substudies A and C: Safety analyses were descriptive. For each AE, the percentage of participants reporting the AE was summarized by study group. AEs and SAEs were categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms.

6.2.10 Study Population and Disposition

Substudy A

The substudy started on July 1, 2021. The analyses presented in this report were based on a data cutoff date of February 8, 2022. The safety population included a total of 10,125 participants: BNT162b2 (Original) group, n=5081; placebo group, n=5044. All 11 (0.1%) participants excluded from the safety population were excluded because they did not receive study intervention. Study participant withdrawal was 0.6% in the BNT162b2 (Original) group and 1.9% in the placebo groups, of which 0.7% was voluntary. The median blinded follow-up time after study vaccination was 2.9 months (0.4, 7.5). The duration of follow-up from Dose 3 vaccination to the cutoff date was a median time of 7.1 months (1.0, 8.0).

Substudy C

The substudy started on December 20, 2021. The analyses presented in this report were based on a data cutoff date of July 14, 2022. A total of 140 participants were randomized 1:1 to receive a study vaccination with BNT162b2 (Original) 10 µg or 30 µg administered as Dose 3. All randomized participants received study vaccination out of which 138 (98.6%) participants completed the 1-month post-dose visit while 2 (1.4%) participants withdrew from the study (lost to follow-up). The safety population included 140 participants: BNT162b2 (Original), 10 µg group, n=75; BNT162b2 (Original), 30 µg group, n=65. No participants were excluded from the safety population.

6.2.10.1 Populations Enrolled/Analyzed

For Substudies A and C, the safety population consisted of participants who received the study intervention.

6.2.10.1.1 Demographics

Substudy A

Demographic characteristics for all participants in the safety population 16-55 years of age were similar in the BNT162b2 (Original) and placebo groups (Table 15). Overall, 79.0% of participants were White, 9.2% were Black or African American, 5.5% were Asian, and 4.0% were multiracial, and 14.9% were Hispanic/Latino. The median age at the time of study vaccination was 53.0 years of age, and 49.1% of participants were male. Enrollment of 85.9% of study participants was from U.S. sites. Obese participants made up 35.9% of the safety

population. At the time of Dose 3, 5.4% were baseline SARS-CoV-2 positive. During the blinded follow up period, the median time from Dose 2 of the primary series of BNT162b2 (Original) to receipt of Dose 3 vaccination was 10.8 months (range 5.0, 12.6).

Table 15. Demographic Characteristics, Participants ≥16 Years of Age, Safety Population, Study C4591031, Substudy A

Characteristic	BNT162b2 (Original) (30 µg) N=5081 n (%)	Placebo N=5044 n (%)	Total N=10125 n (%)
Sex	-	-	-
Male	2457 (48.4)	2518 (49.9)	4975 (49.1)
Female	2624 (51.6)	2526 (50.1)	5150 (50.9)
Race	-	-	-
White	3997 (78.7)	4003 (79.4)	8000 (79.0)
Black or African American	471 (9.3)	460 (9.1)	931 (9.2)
American Indian or Alaska Native	86 (1.7)	91 (1.8)	177 (1.7)
Asian	288 (5.7)	269 (5.3)	557 (5.5)
Native Hawaiian or other Pacific Islander	8 (0.2)	11 (0.2)	19 (0.2)
Multiracial	208 (4.1)	196 (3.9)	404 (4.0)
Not reported	23 (0.5)	14 (0.3)	37 (0.4)
Ethnicity	-	-	-
Hispanic/Latino	760 (15.0)	751 (14.9)	1511 (14.9)
Non-Hispanic/non-Latino	4309 (84.8)	4285 (85.0)	8594 (84.9)
Not reported	12 (0.2)	8 (0.2)	20 (0.2)
Country	-	-	-
Brazil	580 (11.4)	584 (11.6)	1164 (11.5)
South Africa	134 (2.6)	134 (2.7)	268 (2.6)
U.S.	4367 (85.9)	4326 (85.8)	8693 (85.9)
Age in years	-	-	-
16-55	2823 (55.6)	2797 (55.5)	5620 (55.5)
>55	2258 (44.4)	2247 (44.5)	4505 (44.5)
16-17	46 (0.9)	44 (0.9)	90 (0.9)
18-55	2777 (54.7)	2753 (54.6)	5530 (54.6)
56-64	1083 (21.3)	1059 (21.0)	2142 (21.2)
65+	1175 (23.1)	1188 (23.6)	2363 (23.3)
Mean (SD) (years)	51.8 (15.24)	51.7 (15.33)	51.7 (15.28)
Median (years)	53.0	53.0	53.0
Min, max (years)	(16, 86)	(16, 87)	(16, 87)
Baseline SARS-CoV-2 status	-	-	-
Positive[a]	289 (5.7)	262 (5.2)	551 (5.4)
Negative[b]	4785 (94.2)	4775 (94.7)	9560 (94.4)
Unknown	7 (0.1)	7 (0.1)	14 (0.1)

Characteristic	BNT162b2 (Original) (30 µg) N=5081 n (%)	Placebo N=5044 n (%)	Total N=10125 n (%)
Body mass index (BMI	-	-	-
Underweight (<18.5 kg/m2)	57 (1.1)	49 (1.0)	106 (1.0)
Normal weight (≥18.5-24.9 kg/m2)	1431 (28.2)	1457 (28.9)	2888 (28.5)
Overweight (≥25.0-29.9 kg/m2)	1769 (34.8)	1728 (34.3)	3497 (34.5)
Obese (≥30.0 kg/m2)	1822 (35.9)	1810 (35.9)	3632 (35.9)
Missing	2 (0.0)	0	2 (0.0)
Comorbidities[c]	-	-	-
Yes	2460 (48.4)	2468 (48.9)	4928 (48.7)
No	2621 (51.6)	2576 (51.1)	5197 (51.3)

Source: Adapted from STN125742/276/8, c4591031-suba-interim-mth6-report-body.pdf, Table 8
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives. N, number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations; n, number of participants with the specified characteristic.
a. Positive, N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
b. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index category or BMI ≥30 kg/m2.
Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
Abbreviations: N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; N, number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations; n, number of participants with the specified characteristic.

Substudy C

Demographics and baseline characteristics of the safety population are presented in Table 16. The total safety population consisted of 75.0% White, 14.3% Black or African American, 8.6% Asian, with <1% in other race subgroups; 18.6% of participants were Hispanic/Latino. Sex was 50% male and 50% female. The median age at study vaccination was 14.0 years of age; 85.0% of participants were 12- 15 years of age, and 15.0% of participants were 16 through 17 years of age. A total of 15.7% of participants were obese, and 36.4% had evidence of prior SARS-CoV-2 infection before Dose 3 vaccination. The median time from completing Dose 2 of the primary series of BNT162b2 (Original), 30 µg to receipt of Dose 3 was 13.2 months, with most participants (67.9%) receiving Dose 3 ≥1 year after the primary series.

Table 16. Demographic Characteristics, Participants 12-17 Years of Age, Safety Population, Study C4591031, Substudy C

Characteristic	BNT162b2 (Original) (10 µg) N=75 n[b] (%)	BNT162b2 (Original) (30 µg) N=65 n[b] (%)	Total N=140 n[b] (%)
Sex	--	--	--
Male	38 (50.7)	32 (49.2)	70 (50.0)
Female	37 (49.3)	33 (50.8)	70 (50.0)
Race	--	--	--
White	55 (73.3)	50 (76.9)	105 (75.0)
Black or African American	11 (14.7)	9 (13.8)	20 (14.3)
Asian	7 (9.3)	5 (7.7)	12 (8.6)
Native Hawaiian or other Pacific Islander	0	1 (1.5)	1 (0.7)
Multiracial	1 (1.3)	0	1 (0.7)
Not reported	1 (1.3)	0	1 (0.7)

Characteristic	BNT162b2 (Original) (10 µg) N=75 n[b] (%)	BNT162b2 (Original) (30 µg) N=65 n[b] (%)	Total N=140 n[b] (%)
Ethnicity	--	--	--
Hispanic/Latino	15 (20.0)	11 (16.9)	26 (18.6)
Non-Hispanic/non-Latino	59 (78.7)	53 (81.5)	112 (80.0)
Not reported	1 (1.3)	1 (1.5)	2 (1.4)
Country	--	--	--
U.S.	75 (100.0)	65 (100.0)	140 (100.0)
Age group (at Dose 3)	--	--	--
12-15 Years	61 (81.3)	58 (89.2)	119 (85.0)
16-17 Years	14 (18.7)	7 (10.8)	21 (15.0)
Age at Dose 3 (years)	--	--	--
Mean (SD)	14.4 (1.25)	14.2 (1.10)	14.3 (1.19)
Median	14.0	14.0	14.0
Min, max	(12, 17)	(12, 17)	(12, 17)
Obese[a]	--	--	--
Yes	12 (16.0)	10 (15.4)	22 (15.7)
No	63 (84.0)	55 (84.6)	118 (84.3)
Pre–Dose 3 SARS-CoV-2 status	--	--	--
Positive[b]	23 (30.7)	28 (43.1)	51 (36.4)
Negative[c]	51 (68.0)	37 (56.9)	88 (62.9)
Unknown	1 (1.3)	0	1 (0.7)
Time (in months) from BNT162b2, 30 µg Dose 2 to Dose 3	--	--	--
Mean (SD)	11.9 (2.69)	12.5 (2.43)	12.2 (2.58)
Median	13.1	13.3	13.2
Min, max	(6.5, 17.3)	(6.5, 16.9)	(6.5, 17.3)
≥6 to <8 Months	3 (4.0)	4 (6.2)	7 (5.0)
≥8 to <10 Months	24 (32.0)	10 (15.4)	34 (24.3)
≥10 to <12 Months	3 (4.0)	1 (1.5)	4 (2.9)
≥12 Months	45 (60.0)	50 (76.9)	95 (67.9)

Source: Adapted from STN125742/276, c4591031-ssc-interim-mth1-12-17years of age-report-body.pdf, Table 7
Notes:
a. For participants ≥16 years of age, obesity is defined as BMI ≥30 kg/m^2. For participants 12-15 years of age, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
b. Positive N-binding antibody result at booster (third) dose visit or medical history of COVID-19.
c. Negative N-binding antibody result at booster (third) dose visit and no medical history of COVID-19.
Abbreviations: N, number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations; n (%), number and percentage of participants with the specified characteristic; N-binding, SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

For Substudies A and C, the percentage of participants who were obese and who had co-morbidities are summarized in Section 6.2.10.1.1. Also, in Substudy A, 50 participants were HIV positive.

6.2.10.1.3 Subject Disposition

Substudy A

During the blinded placebo-controlled follow-up period, 99.0% of participants completed the 1-month telephone contact (Table 17). The most cited reason for withdrawal from the study was voluntary withdrawal of participant consent (0.7%).

Participants who were randomized to receive placebo at the booster vaccination visit were offered the opportunity to receive BNT162b2 (Original) if indicated by the outcome of the interim analyses or at the discretion of the study sponsor agent, and the participants' study intervention assignments were unblinded if the information was not already available and the participants were thereafter followed in an open-label manner. Of the participants who were originally randomized to BNT162b2 (Original), 3.6% withdrew from the study during the open-label period. The most common reason cited was "other" (2.0%), which was mostly due to participants enrolling in Study C4591031 Substudy D.

Of the participants originally randomized to the placebo group, 87.6% received BNT162b2 (Original), 30 µg Dose 3. After unblinding and before administration of BNT162b2 (Original) Dose 3, 6.6% of participants withdrew from the study. Of the participants in this group who received BNT162b2 (Original) Dose 3, 4.7% were withdrawn from the study; the most common reason cited was "other" (4.3%), which was mostly due to participants enrolling in Study C4591031 Substudy D.

During the open label period, for participants who were originally randomized to BNT162b2 (Original), the frequency of withdrawal was 5.2% in the younger age group (16-55 years of age) and 1.7% in the older age group (>55 years of age).

Table 17. Disposition of All Randomized Participants, ≥16 Years of Age, Study C4591031, Substudy A

Disposition	BNT162b2 (Original) (30 µg) N=5088 n (%)	Placebo N=5048 n (%)	Total N=10136 n (%)
Randomized	5088 (100)	5048 (100)	10136 (100)
Not vaccinated with booster dose	6 (0.1)	5 (0.1)	11 (0.1)
Blinded follow-up period	-	-	-
Vaccinated with booster dose	5082 (99.9)	5043 (99.9)	10125 (99.9)
Completed the 1-month telephone contact	5067 (99.6)	4967 (98.4)	10034 (99.0)
Open-label follow-up period	-	-	-
Unblinded after booster vaccination and before or on the same day of the 1-month telephone contact	7 (0.1)	50 (1.0)	57 (0.6)
Unblinded after the 1-month telephone contact	4498 (88.4)	4852 (96.1)	9350 (92.2)
Originally randomized to BNT162b2	4505 (88.5)	-	-
Completed the 1-month telephone contact	6 (0.1)	-	-
Completed the 6-month visit	3992 (78.5)	-	-

Disposition	BNT162b2 (Original) (30 µg) N=5088 n (%)	Placebo N=5048 n (%)	Total N=10136 n (%)
Originally randomized to placebo	-	4902 (97.1)	-
Withdrawn from the study after unblinding and before BNT162b2 vaccination	-	334 (6.6)	-
Vaccinated with the booster dose (BNT162b2 [30 µg])[a]	-	4420 (87.6)	-
Completed the 1-month telephone contact after BNT162b2 vaccination[a]	-	4366 (86.5)	-

Source: Adapted from STN125742/276/8, c4591031-suba-interim-mth6-report-body.pdf, Table 3
Note: Human immunodeficiency virus (HIV)-positive participants are included in this summary but not included in the analyses of the overall study objectives.
Note: Blinded follow-up period was censored to the cutoff date or the day before date of unblinding (per protocol) or the day before date of receiving COVID-19 vaccine off study, whichever date was earlier.
a. Includes one subject whose vaccine (as administered) could not be determined.
Abbreviations: N, number of randomized participants in the specified group, or the total sample. This value is the denominator for the percentage calculations; n (%), number and percentage of participants with the specified characteristic.

Protocol Deviations
Across vaccine groups, the most reported (3.0% total) type of important PD was related to receipt of other nonstudy coronavirus vaccine at any time during the study, which was reported in 0.8% of BNT162b2 (Original) participants and 5.2% of placebo participants. The next most reported (1.2% total) important PD was related to the inclusion criteria requirement for receipt of the 2-dose primary series of BNT162b2 (Original), 30 µg given 19-42 days apart, with Dose 2 being at least 175 days before booster study Visit 1 (Day 1).

Substudy C
A total of 140 received 1 study vaccination with BNT162b2 (Original) 10 µg or 30 µg administered as Dose 3. All randomized participants received study vaccination and 98.6% completed the 1-month post-dose visit. In the BNT162b2 (Original), 30 µg group, 13.8% (n=9) of participants did not meet an inclusion criterion.

6.2.11 Efficacy Analyses

Substudies A and C: efficacy and immunogenicity analyses were not reviewed because this study was viewed primarily as a safety study to support single dose use.

6.2.12 Safety Analyses

Reviewer Comment*: Adverse events of clinical interest (AECI), such as those requested by FDA and those on the CDC list of AESIs for COVID-19, including anaphylaxis/hypersensitivity, myocarditis/pericarditis, lymphadenopathy, Bell's palsy, and tinnitus, were summarized in a subsection entitled Adverse Events of Clinical Interest. These AEs, according to the protocol, were reported as AE or SAE, depending on whether the event was categorized non-serious or serious, or an AESI.*

6.2.12.1 Methods

See Section 6.2.7

6.2.12.2 Overview of Adverse Events

Substudy A
An overview of AEs from booster vaccination to the unblinding date for participants during the blinded placebo-controlled follow-up period is shown in Table 18. A greater proportion of

participants in the BNT162b2 (Original) group (26.4%) experienced any AE compared with the placebo group (7.8%), mainly due to unsolicited AEs corresponding to reactogenicity symptoms. Any severe AEs or SAEs were reported across the BNT162b2 (Original) and placebo groups in ≤1.1% and ≤0.8%, respectively. AEs leading to withdrawal were reported in 1 participant in the placebo group (SAEs of metastatic cancer with renal, diaphragm, and hepatic involvement), and none in the BNT162b2 (Original) group. Two participants in the placebo group died due to SAEs (pulmonary embolism, *Pneumocystis jirovecii* pneumonia) that were consider by the study investigator and FDA to be unrelated to BNT162 (Original) vaccination.

Table 18. Incidence Rates of At Least 1 Adverse Event from Booster Vaccination to Unblinding Date, Blinded Follow-Up Period, Safety Population, Study C4591031, Substudy A

Adverse Event	BNT162b2 (Original) (30 µg) N=5055 n[a] (%) (95% CI[b])	Placebo N=5020 n[a] (%) (95% CI[b])
Any event	1335 (26.4) (25.2, 27.6)	394 (7.8) (7.1, 8.6)
Any serious adverse event	39 (0.8) (0.5, 1.1)	35 (0.7) (0.5, 1.0)
Any nonserious adverse event	1313 (26.0) (24.8, 27.2)	377 (7.5) (6.8, 8.3)
Any adverse event leading to withdrawal	0 (0.0) (0.0, 0.1)	1 (0.0) (0.0, 0.1)
Death	0 (0.0) (0.0, 0.1)	2 (0.0) (0.0, 0.1)

Source: Adapted from: STN125742/276/8 c4591031-suba-interim-mth6-report-body.pdf Table 19
Notes:
a. For "any event," n=number of participants reporting at least 1 occurrence of any event.
b. 2-Sided CI based on Clopper-Pearson.
Abbreviations: N, number of participants in the specified group; n, number of participants reporting at least 1 occurrence of the specified event category; CI, confidence interval

Subgroup analyses of BNT162b2 (Original) Dose 3 vaccination AEs to the unblinding date for participants during the blinded placebo-controlled follow-up period by age, sex, race and ethnicity, were as follows:

- 28.6% in the younger (16-55 years of age) group and 23.6% in the older (>55 years of age) group.
- 23.3% in male participants and 29.4% in female participants.
- 25.0% to 36.6% across race subgroups.
- 37.3% in Hispanic/Latino participants and 24.5% in non-Hispanic/non-Latino participants, mainly due to reactogenicity events reported in these subgroups.
- Frequency of any AEs varied between the countries; however, the pattern of differences observed between BNT162b2 (Original) and placebo groups was similar within each country. In order of increasing frequency, any AEs were reported by country as follows: South Africa, 6.5%; U.S., 21.0%; and Brazil 71.4%. Related AEs (mainly reactogenicity events) made up most of the reported AEs.
- The frequency of any AE after BNT162b2 (Original) Dose 3 vaccination was 25.1% in baseline SARS-CoV-2 positive participants (n=283) and 26.5% in baseline SARS-CoV-2 negative participants (n=4765).

Immediate Adverse Events:
The frequencies of immediate AEs (occurring within 30 minutes post-vaccination) reported

after the Dose 3 were similar (BNT162b2 (Original) group, ≤0.3%; placebo group, ≤0.3%). In both study groups, immediate AEs were predominantly reactogenicity events (e.g., IS pain, and headache). One participant in the BNT162b2 (Original) group reported dizziness. In the placebo group, other immediate AEs included nausea, oral paresthesia, chest discomfort, heart rate increased, arthralgia, musculoskeletal discomfort, paresthesia, cold sweat, and flushing.

Unsolicited Adverse Events:
During the blinded placebo-controlled and open-label follow-up periods from BNT162b2 (Original) Dose 3 vaccination to 6 months post-Dose 3 among the BNT162b2 (Original) recipients, 1366 participants (27.3%) who originally received BNT162b2 (Original), had at least 6 months of follow-up time post-Dose 3, and reported AEs during this time. Commonly reported AEs included reactogenicity events in the following system organ class (SOC): 21.6% in *General disorders and administration site conditions*, 7.2% in *Musculoskeletal and connective tissue disorders*, 6.0% in *Nervous system disorders*, and 2.9% in *Blood and lymphatic system disorders*. A higher frequency of reported unsolicited AEs among BNT162b2 (Original) recipients compared with placebo recipients was primarily attributed to events that are consistent with AE solicited in the 7 days after BNT162b2 (Original) Dose 3 vaccination. Also, overall, lymphadenopathy was reported at a higher frequency in Study C4591031 participants post-Dose 3 vaccination with BNT162b2 (Original) (2.7%) compared with participants in Study C4591001 after the two-dose primary series of BNT162b2 (Original) (0.4%); 4.0% of participants were 16-55 years of age and 1.0% of participants were >55 years of age.

Substudy C
An overview of AEs from booster vaccination to the unblinding date for participants during the blinded placebo-controlled follow-up period is shown in Table 19. The frequencies of AEs were similar among participants with evidence of prior SARS-CoV-2 infection at the time of Dose 3 and those without evidence of prior infection at the time of Dose 3 (7.1% vs. 8.1%).

Table 19. Participants Reporting at Least 1 Adverse Event from Booster Dose (Dose 3) Through the Data Cutoff Date, Participants 12-17 Years of Age, Safety Population, Study C4591031, Substudy C

Adverse Event	BNT162b2 (Original), 30 µg (N[a]=65) n[b] (%)
Any event	9 (13.8)
Any serious adverse event	1 (1.5)
Any nonserious adverse event	9 (13.8)

Source: Adapted from: STN125742/559 c4591031-ssc-interim-mth1-12-17years of age-report-body.pdf Table 14.29
Notes: From the time of the BNT162b2 (Original) booster dose to the data cutoff (July 1, 2023), there were no AEs leading to premature study withdrawal and no deaths reported; For "any adverse event," n=number of participants reporting at least 1 occurrence of any event.
Abbreviations: N, number of participants in the specified group; n, number of participants reporting at least 1 occurrence of the specified adverse event category

Immediate AEs:
No immediate AEs (occurring within 30 minutes post-vaccination) were reported after Dose 3 administration for both dose level groups.

Unsolicited AEs:
During the time period from administration of Dose 3 to 1-month post-Dose 3, 7.7% (n=5) of participants in the BNT162b2 (Original), 30 µg group reported an unsolicited AE (Attention Deficit Hyperactivity Disorder (n=2), rhinitis (n=1), dysmenorrhea (n=1), and mild syncope (n=1) on Day 8 following Dose 3 vaccination that resolved within 1 day). Additional AEs reported after

1-month post-Dose 3 and up to the data cutoff date included nonserious events of depression (n=2), COVID-19 (n=1), cellulitis (n=1), and foot fracture (n=1).

Reviewer Comment*: The reported AEs were consistent with medical conditions that are common to the population studied (12-17 years of age).*

6.2.12.3 Deaths

Substudy A

There were nine participants who died during the study as of the data cutoff date, including three in the younger (16-55 years of age) and six in the older (>55 years of age) age groups. All these deaths were assessed by the investigator and this clinical reviewer as not related to study intervention.

During the blinded placebo-controlled follow-up period, two participants in the placebo group died: one placebo participant had an unrelated SAE of pulmonary embolism, and one participant with AIDS had an unrelated SAE of *pneumocystis jirovecii* pneumonia.

From the unblinding date to the data cutoff date of the open-label follow-up period, there were:

- three deaths in BNT162b2 (Original) participants, due to unrelated events of myocardial infarction, infection, and death (of unknown causes) as assessed by the investigator and FDA.
- four deaths in original placebo participants who then received BNT162b2 (Original), due to unrelated events of multiple injuries (received in a car accident), ill-defined disorder (death of unknown causes), adrenocortical carcinoma (with metastasis; SAE), and sudden cardiac death.

Substudy C

There were no deaths as of the data cutoff date.

6.2.12.4 Nonfatal Serious Adverse Events

Substudy A

A total of 74 participants reported at least 1 SAE during the time of administration of Dose 3 to the unblinding date for participants during the blinded placebo-controlled follow-up period, (BNT162b2 (Original) group, n=39; placebo group, n=35). All but three of the BNT162b2 (Original) participant SAEs were assessed by the investigator and the FDA as not related to study intervention. For these unrelated SAEs, the SOC with the highest frequency of report was *Infections and infestations* (n=8: e.g., cholangitis 139 days after vaccination, gastroenteritis 149 days after vaccination, and abdominal sepsis 84 days after vaccination) followed by *Neoplasms* (n=6: e.g., meningioma 149 days after vaccination, ductal breast cancer 134 days after vaccination, and uterine cancer 90 days after vaccinations). The SOC SAE numbers were balanced compared with the placebo group.

SAEs were assessed as related for three participants, all of whom were in the BNT162b2 (Original) group: tachycardia (n=1) and increased hepatic enzymes (n=2).

Additionally, the following unrelated SAEs were reported during the blinded follow-period and were included with the AESIs: appendicitis (n=2), appendicitis perforated (n=1), and septic shock (n=1).

Substudy C
From booster vaccination to data cutoff date (July 14, 2022,) one participant in the BNT162b2 (Original), 30 µg group reported a severe SAE of constipation on Day 63 after Dose 3 vaccination that resolved within 6 days. The event was assessed by the investigator and the FDA as not related to study intervention.

6.2.12.5 Adverse Events of Special Interest

Substudy A
AESI, such as those requested by FDA and those on the CDC list of AESIs for COVID-19, were reported in 327 (6.5%) participants. The most frequently reported AESI was pyrexia (n=251, 5.0%), followed by arthralgia (n=42, 0.8%). During the blinded placebo-controlled follow-up period, lymphadenopathy was reported in 135 participants (2.7%). All cases of lymphadenopathy were mild or moderate in severity, and the majority were in the axilla or cervical nodes. Median onset was 2.0 days after Dose 3 vaccination. Lymphadenopathy frequency was higher in younger (16-55 years of age) compared with older (>55 years of age) participants (4.0% vs 1.0%), and higher in female than in male participants (3.5% vs 1.8%).

Substudy C
As of the data cutoff date there were no cases reported of lymphadenopathy, rash, myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), appendicitis, or anaphylaxis (or hypersensitivity). No pregnancies were reported after receipt of the Dose 3 up to the data cutoff date.

6.2.12.6 Clinical Test Results

Clinical laboratory evaluations were not performed in this study.

6.2.12.7 Dropouts and/or Discontinuations

Substudy A
In total, there were six Dose 3 recipients with any AE leading to withdrawal, as of the data cutoff date. None of these events were assessed as related.

Substudy C
There were no discontinuations due to AEs as of the data cutoff date.

6.2.13 Study Summary and Conclusions

Substudy A
In this Substudy, a total of 10,125 participants ≥16 years of age received either BNT162b2 (Original), 30 µg Dose 3 (n=5081) or placebo (n=5044). Data showed Dose 3 administration was generally safe with reactogenicity assessments and adverse reactions similar to the safety data previously observed with BNT162b2 (Original) primary series. Safety data provided in the interim report included the blinded placebo-controlled portion of the study and the open-label follow-up periods from Dose 3 vaccination to 6-months post-Dose 3 vaccination of BNT162b2 (Original) participants with at least 6-months follow-up. Overall, FDA review of AEs (including SAEs, AESIs, and AEs of clinical interest) collected at least 6 months of follow-up post-Dose 3 in 5000 participants originally randomized to BNT162b2 (Original), comprising the combined blinded and open-label periods, showed no new safety concerns associated with booster dosing and were consistent with the known safety and tolerability profile following the 2-dose primary series. Both lymphadenopathy and rash were more frequently reported after BNT162b2 (Original) Dose 3 as compared with placebo, and both of these events are known to be adverse reactions of BNT162b2 (Original). No cases of vaccine-associated anaphylaxis, hypersensitivity, myocarditis/pericarditis, or Bell's palsy after BNT162b2 (Original) vaccination in the study were

reported up to the data cutoff date. Subgroup analyses did not suggest any specific safety concerns with regard to age, sex, race, ethnicity, country, or prevaccination SARS-CoV-2 status.

Substudy C
The safety profile of BNT162b2 (Original), 30 µg in participants 12-17 years of age was generally acceptable and consistent with results reported for the primary series (STN 125742.0 FDA clinical review memo). The frequencies of AEs were similar among participants with evidence of prior SARS-CoV-2 infection at the time of Dose 3 and those without evidence of prior infection at the time of Dose 3.

6.3 Study C4591001

NCT04368728
"A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study To Evaluate The Safety, Tolerability, Immunogenicity, And Efficacy Of SARS-Cov-2 RNA Vaccine Candidates Against COVID-19 In Healthy Individuals."

Study Overview
Study C4591001 safety data (SAEs, AESIs) provided supportive information for single dose use of COMIRNATY, including Comirnaty (2023-2024 Formula), in individuals ≥12 years of age who were previously vaccinated with a COVID-19 vaccine. The study design as described herein reflects objectives, endpoints, and monitoring pertaining to safety evaluations following BNT162b2 (Original), 30 µg Dose 3 in participants ≥12 years of age who completed a 2-dose primary series of BNT162b2 (Original). In this study, BNT162b2 (Original), 30 µg Dose 3 was administered to participants 12-55 years of age at least 6 months post-BNT162b2 (Original) Dose 2. A subset of participants 18-55 years of age received a primary series or booster dose(s) of an early version of a modified COVID-19 vaccine, BNT162b2 SA (South Africa; beta variant). Clinical development of modified COVID-19 vaccines containing BNT162b2 (Original) were selected for further development, and therefore only the Phase 2/3 safety data for participants receiving a BNT162b2 (Original), 30 µg Dose 3 are presented in this clinical review.

6.3.1 Objectives

For both age cohorts (12-15, and 18-55 years of age), the safety objective was to describe the safety of BNT162b2 (Original) Dose 3.

The endpoints relevant to this sBLA safety review were:

- AEs from administration of the study vaccination through 1 month postvaccination
- SAEs from administration of the study vaccination through 6 months postvaccination

For the adult cohort (18-55 years of age), the immunogenicity objective was to evaluate the noninferiority of the anti–reference strain immune response (GMR and seroresponse) after BNT162b2 (Original) Dose 3 compared to the response after BNT162b2 (Original) Dose 2, in the same individuals.

6.3.2 Design Overview

Study C4591001 is an ongoing Phase 1/2/3 study of SARS-CoV-2 RNA vaccine candidates; primary objectives, endpoints, and analyses following a 2-dose primary series were reviewed in the BLA (STN 125742). The protocol for this ongoing study was amended over time to include individuals 12-15 years of age, and booster analyses. Following issuance of the EUA for the Pfizer-BioNTech COVID-19 Vaccine, Phase 2/3 participants initially randomized to the placebo

group were offered BNT162b2 (Original) vaccination. Enrollment in the booster portion of the study started March 31, 2021.

Dose 3, 30µg BNT162b2 (Original) was administered to 825 participants 12-15 years of age who had not received Dose 3 of COVID-19 vaccine. The vaccine was administered in an open-label manner. Participants 18-55 years of age who were initially randomized to and completed a 2-dose primary series of BNT162b2 (Original) were rerandomized to receive Dose 3, 30 µg BNT162b2 (Original) (n=306) or BNT162b2SA, 30 µg (n=318), approximately 6 months after Dose 2 of BNT162b2 (Original). Other subsets of participants 18-55 years of age received Dose 3 and Dose 4 of BNT162b2SA or BNT162b2SA as a 2-dose primary series. The duration of safety follow-up after BNT162b2 (Original) Dose 3 was 6 months.

6.3.3 Population

12-15 years of age:
Summarized Inclusion Criteria: individuals 12-15 years of age (Phase 2/3), at the time of receiving Dose 3.

Summarized Exclusion Criteria: Individuals were excluded from the study if they had a medical or psychiatric condition including recent (within past year) or active suicidal ideation/behavior, immunocompromised condition or suspected immunodeficiency, were pregnant or breastfeeding. Individuals were also excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention.

18-55 years of age:
Summarized Inclusion Criteria: individuals 18-55 years of age at the time of Dose 3.

Summarized Exclusion Criteria: Individuals were excluded from the study if they had a medical or psychiatric condition including recent (within past year) or active suicidal ideation/behavior, immunocompromised condition or suspected immunodeficiency, were pregnant or breastfeeding. Individuals were also excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention.

6.3.4 Study Treatments or Agents Mandated by the Protocol

For all participants 12-15 years of age and 18-55 years of age who received BNT162b2 (Original):
Intervention name: BNT162b2 (Original) (BNT162 RNA-LNP vaccine utilizing modRNA)
Unit dose strength: 250 µg/0.5 mL
Dosage Level: 30 µg
Route of Administration: IM injection

6.3.5 Directions for Use

For both age cohorts, detailed instruction for preparing BNT162b2 (Original) are described in the full prescribing information in the Comirnaty PI.

6.3.6 Sites and Centers

This study was conducted at 27 sites in the U.S.

6.3.7 Surveillance/Monitoring

12-15 years of age: solicited local AE or systemic AEs were not assessed. IS reactions and systemic AEs were recorded as unsolicited AEs.

For both age cohorts, safety surveillance for immediate AEs, unsolicited AEs, SAEs and AESIs was the same as Study C4591031. Please see Section 6.2.7.

6.3.8 Endpoints

For both age cohorts, see Section 6.3.1.

6.3.9 Statistical Considerations & Statistical Analysis Plan

12-15 years of age:
In Phase 3, approximately 2000 participants 12-15 years of age were planned to be enrolled based on regulatory requirements for the safety database.

For both age cohorts, descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) were provided for AEs and SAEs from the time of the BNT162b2 (Original) Dose 3 to 1 month post-Dose 3.

18-55 years of age:
Noninferiority was assessed based on the GMR of SARS-CoV-2 neutralizing titers (reference strain) using a 1.5-fold margin and comparison of the point estimate of the GMR to 0.8. Noninferiority was also assessed based on the difference in percentages of participants with a seroresponse using a 10% margin.

6.3.10 Study Population and Disposition

The interim safety data cutoff date for participants 12-15 and 18-55 years of age was November 3, 2022, and November 22, 2021, respectively.

12-15 years of age:
The BNT162b2 (Original) booster safety population included 825 participants 12-15 years of age who previously received the BNT162b2 (Original), 30 µg 2-dose primary series in Phase 2/3 of the study and then a BNT162b2 (Original), 30 µg, Dose 3. For most participants (86.9%), the duration of safety follow-up after Dose 3 was ≥6 months, with a median follow-up time of 9.5 months (range: 1.5 to 10.7 months). The median time between Dose 2 and Dose 3 was 11.2 months (range: 6.3-20.1).

18-55 years of age:
The safety population was comprised of BNT162b2 (Original)-experienced participants rerandomized to receive Dose 3 of BNT162b2 (Original), 30 µg (n=306). One participant did not receive study booster vaccine and was excluded. The median follow-up time after Dose 3 in the BNT162b2 (Original) group was 8.3 months (range: 1.1 to 8.5 months). A total of 298 completed the 6-month post-Dose 3 vaccination visit. The median time between Dose 2 and Dose 3 was 6.8 months (range: 4.8-8.0 months).

The immunogenicity population was comprised of BNT162b2 (Original)-experienced participants rerandomized to receive Dose 3 of BNT162b2 (Original), 30 µg (n=312). Two participants were excluded from the all-available immunogenicity population because they did not have immunogenicity results after vaccination.

6.3.10.1 Populations Enrolled/Analyzed

For both age cohorts, the booster safety population consisted of participants who received at least 1 booster dose of the study intervention.

6.3.10.1.1 Demographics

Table 20. Demographic Characteristics, Phase 2/3 Participants, Booster Safety Population, Study C4591001

Demographic Characteristics	BNT162b2 (Original), 30 µg 12-15 YOA N=825 n (%)	BNT162b2 (Original), 30 µg 18-55 YOA N=306 n (%)
Sex	-	-
Male	407 (49.3)	140 (45.8)
Female	418 (50.7)	166 (54.2)
Race	-	-
White	689 (83.5)	249 (81.4)
Black or African American	38 (4.6)	28 (9.2)
American Indian or Alaska Native	3 (0.4)	2 (0.7)
Asian	62 (7.5)	16 (5.2)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.3)
Multiracial	26 (3.2)	4 (1.3)
Not reported	6 (0.7)	6 (2.0)
Ethnicity	-	-
Hispanic/Latino	89 (10.8)	85 (27.8)
Non-Hispanic/non-Latino	734 (89.0)	219 (71.6)
Not reported	2 (0.2)	2 (0.7)
Country: U.S.	825 (100)	306 (100)
Age at Dose 3 (years)	-	-
Mean (SD)	14.1 (0.80)	41.3 (9.44)
Median	14.0	42.0
Min, max	(13, 15)	(19, 55)
Obese[a]	-	-
Yes	100 (12.1)	-
No	725 (87.9)	-
Body Mass Index	-	-
Underweight (<18.5 kg/m2)	-	1 (0.3)
Normal weight (≥18.5-24.9 kg/m2)	-	82 (26.8)
Overweight (≥25.0-29.9 kg/m2)	-	101 (33.0)
Obese (≥30.0 kg/m2)	-	122 (39.9)

Source: Adapted from: STN125742/559 c4591001-interim-mth6-pd3-12-15years of age-report-body.pdf Table 7; and STN125742/559 c4591001-interim-booster-mth6-g0-g3-report-body.pdf Table 13
Notes: a. Obese in pediatric population is defined as BMI ≥95th percentile from the growth chart. The obese status is based on data collected at Visit 1. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
Abbreviations: N, number of participants in the specified group. This value is the denominator for the percentage calculations; n (%), number and percentage of participants with the specified characteristic.

12-15 years of age Group:
Of the 825 participants 12-15 years of age, 83.5% were White, with 4.6% Black or African American participants (Table 20). There were 10.8% Hispanic/Latino participants. At the time the Dose 3 was administered, the median age was 14.0 years (range 13-15 years), and 49.3% of participants were male. Obese participants made up 12.1% of the booster safety population.

18-55 years of age Group:
Of the 306 participants 18-55 years of age who rerandomized to receive BNT162b2 (Original) Dose 3, 82.2% were White, with 9.6% Black or African American participants, 5.3% Asian participants, and other racial groups comprising ≤1.4% each (Table 20). There were 25.6% Hispanic/Latino participants. The median age at the time of the Dose 3 was 43.0 years, and 53.0% of participants were female. Obese participants made up 37.8% of the safety population.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

For both age cohorts, the percentage of participants with co-morbidities are presented in Table 20.

6.3.10.1.3 Subject Disposition

Table 21. Participant Disposition, Phase 2/3 Participants, Booster Safety Population, Study C4591001

Participant Disposition	BNT162b2 (Original), 30 µg 12-15 YOA N=825 n (%)	BNT162b2 (Original), 30 µg 18-55 YOA N=312 n (%)
Received Dose 3 vaccination	825 (100)	312 (100)
Completed Dose 3 vaccination period[a]	819 (99.3)	309 (99.0)
Completed 6-month post–Dose 3 visit	-	298 (95.5)

Source: Adapted from: STN125742/559 c4591001-interim-mth6-pd3-12-15years of age-report-body.pdf Table 4, 36 and STN125742/559 c4591001-interim-booster-mth6-g0-g3-report-body.pdf Table 9
Notes: a. Booster vaccination period: from booster vaccination to the 1-month follow-up visit after the booster vaccination
Abbreviations: N, number of assigned subjects in the specified group; n (%), number and percentage of subjects with the specified characteristic

12-15 years of age:
Among the 825 participants who received a BNT162b2 (Original) Dose 3 in Phase 2/3, 819 (99.3%) completed 1-month postvaccination follow-up (Table 21). After receiving BNT162b2 (Original) Dose 3, 176 participants withdrew from the study, including 25 (3.0%) who were lost to follow-up. There were 124 (15.0%) participants withdrawn from the study for “Other” reasons, mainly due to enrolling into another study during the follow-up phase (n=122). The most frequently reported PD was receipt of other non-study coronavirus vaccine during the study (2.5%) of participants. The most reported (3.0% total) type of important PD was related to receipt of other nonstudy coronavirus vaccine at any time during the study, which was reported in 2.5% of participants (21 all in September and October of 2022). The next most reported (0.2% total) important PD was related to the investigational product (IP); two participants received an IP that was deemed not suitable for use.

18-55 years of age:
Among the 312 participants randomized to receive BNT162b2 (Original) Dose 3, all received the booster and 309 (99%) completed 1 month follow up (Table 21). There were 15 (4.8%) participants who were withdrawn from the study, and most were because of withdrawal by the participant (n=9 [2.9%]), or they were lost to follow-up (n=5 [1.6%]). The most frequently reported (n=16, 5.1% total) PD was related to visit schedule (Visit 301 was conducted outside of the protocol specified window). Thirty-four participants were excluded from the evaluable immunogenicity population due to PD (n=28), not receiving the booster vaccine (n=6), and not having one valid immunogenicity result within 28-42 days of booster (n=6) resulting in an evaluable immunogenicity population of 278.

6.3.11 Immunogenicity Analyses

Immunogenicity analyses were not included in the sBLA package for participants 12-15 years of age. Key immunogenicity analyses for participants 18-55 years of age are noted below.

6.3.11.1 Analyses of Primary Immunogenicity Endpoints

Noninferiority of Responses (GMR, SRR) at 1 Month After BNT162b2 (Original) Dose 3 compared to 1 Month After BNT162b2 (Original) Dose 2: USA_WA1/2020 reference strain
The noninferiority criteria based on GMR and SRR with the USA_WA1/2020 reference strain were met.

The GMR analysis reported in the booster interim CSR, dated 23 August 2021 were reanalyzed based on the revalidated LLOQ value of 41. Among BNT162b2 (Original)-experienced participants without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 3, the SARS-CoV-2 NT50 GMR with the USA_WA1/2020 reference strain at 1-month post-Dose 3 was noninferior to 1-month post-Dose 2 (GMR: 3.26 [2-sided 97.5% CI: 2.76, 3.86], n=212). Among BNT162b2 (Original)-experienced participants without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 3, ≥99.2% of participants had seroresponse to the USA_WA1/2020 reference strain at 1-month post-Dose 3 compared with ≥94.4% of participants 1-month post-Dose 2. Seroresponse for a participant was defined as achieving a ≥4-fold rise in NT50 from baseline (before Dose 1). The difference in percentage of participants with seroresponse met the 10% noninferiority margin (4.5% [2-sided 97.5% CI: 1.0%, 7.9%], n=200).

6.3.12 Safety Analyses

6.3.12.1 Methods

Please see Sections 6.3.7 and 6.2.7.

Reviewer Comment: *AESIs analyses were provided in the interim report but were not a pre-specified endpoint. AECI, such as those requested by FDA and those on the CDC list of AESIs for COVID-19, including anaphylaxis/hypersensitivity, myocarditis/pericarditis, lymphadenopathy, Bell's palsy, and tinnitus, were summarized in a subsection entitled Adverse Events of Clinical Interest. These AEs, according to the protocol, reported as AE or SAE, depending on whether the event was categorized non-serious or serious, or an AESI.*

6.3.12.2 Overview of Adverse Events

Table 22. Participants Reporting at Least 1 Adverse Event from Booster Dose to Cutoff Date, Phase 2/3 Participants, Booster Safety Population, Study C4591001

Adverse Event	BNT162b2 (Original), 30 µg 12-15 YOA N[a]=825 n (%)	BNT162b2 (Original), 30 µg 18-55 YOA N[a]=306 n (%)
Any adverse event	161 (19.5)	46 (15.0)
Any serious adverse event	6 (0.7)	0
Any nonserious adverse event	158 (19.2)	46 (15.0)

Source: Adapted from: STN125742/559 c4591001-interim-mth6-pd3-12-15years of age-report-body.pdf Table 10, p45 and STN125742/559 c4591001-interim-booster-mth6-g0-g3-report-body.pdf Table 27
Note: From the time of the BNT162b2 (Original) booster dose to the data cutoff (November 22, 2021), there were no AEs leading to premature study withdrawal and no deaths reported.
For "any adverse event," n=number of subjects reporting at least 1 occurrence of any adverse event.
Abbreviations: N, number of subjects in the specified group; n, number of subjects reporting at least 1 occurrence of the specified event category.

12-15 years of age:
From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, the unsolicited AEs reported were mainly events that were consistent with adverse reactions solicited in the 7 days postvaccination. The most common unsolicited AE was IS pain in 8.0% participants. Lymphadenopathy was reported in 1.0% participants.

From BNT162b2 (Original) Dose 3 to the data cutoff date, the number of BNT162b2 (Original) participants with any AE was 161 (19.5%). There were 9 additional BNT162b2 (Original) participants that reported any AE beyond the 1-month post-Dose 3 follow-up visit. The additional events were assessed by the investigator and FDA as unrelated to vaccination and included five SAEs. Please see Section 6.3.12.4 for further description of the SAEs.

18-55 years of age:
From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, 46 (15.0%) participants reported at least 1 AE (Table 22), of which 25 (8.2%) were assessed by the study investigator and the FDA as related to vaccination. At the 6-month follow-up visit, an additional 5 participants (total 51 [16.7%]) reported at least 1 AE, including 2 participants who reported a SAE. No AEs leading to withdrawal or deaths were reported up to the 6-month follow-up visit.

Immediate Adverse Events
No immediate events were reported within 30 minutes after the BNT162b2 (Original) Dose 3.

Unsolicited Adverse Events
From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, the most frequently reported unsolicited AE was lymphadenopathy (16 [5.2%] participants). Among the 25 (8.2%) participants with AEs assessed by the investigator and the FDA as related to study intervention, most were lymphadenopathy or reactogenicity events.

The AE frequencies in SOCs for the most common terms were:
- *Blood and lymphatic system disorders*: 5.2% (n=16).
- *General disorders and administration site conditions*: 2.9% (n=9).
- *Musculoskeletal and connective tissue disorders*: 2.3% (n=7).
- *Gastrointestinal disorders*: 1.3% (n=4).

6.3.12.3 Deaths

For both age cohorts, no deaths were reported from the time of the BNT162b2 (Original) Dose 3 to the data cutoff date (November 03, 2022, for 12-15 years of age, November 22, 2021, for 18-55 years of age).

6.3.12.4 Nonfatal Serious Adverse Events

12-15 years of age:
From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, three SAEs were reported by two participants (one participant reported depression, one participant reported suicidal ideation and suicide attempt) and were assessed by the investigator and FDA as unrelated to the vaccine. For both participants, depression was a pre-existing condition and the SAEs occurred 7 days after vaccination and on the day of vaccination respectively.

From the time of the BNT162b2 (Original) booster dose to the data cutoff date, an additional five SAEs were reported by four participants (pectus excavatum, epiphyseal fracture, and suicide ideation; post-traumatic skull fracture and subdural hematoma in the same participant). The

onset of the SAEs ranged from 97-129 days after Dose 3; all the SAEs were assessed by the investigator as unrelated to the study vaccine.

18-55 years of age:
From the time of the BNT162b2 (Original) Dose 3 to the 6-month follow-up visit, two participants reported at least one SAE (≤0.7%). One participant reported ovarian cancer 41 days after vaccination, and another reported an acute myocardial infarction 62 days after vaccination; both were assessed by the investigator and FDA as unrelated to the vaccine.

6.3.12.5 Adverse Events of Special Interest

12-15 years of age: no myocarditis or pericarditis was reported up to the data cutoff date.

18-55 years of age:
There were 2.0% (n=6) BNT162b2 (Original)-experienced participants rerandomized to receive BNT162b2 (Original) Dose 3 who reported seven AESIs: rash (n=2), acute myocardial infarct (n=1) (61 days after vaccine), contusion (n=1), face swelling (n=1), nonspecific swelling (n=1), and chest pain (n=1).

6.3.12.6 Clinical Test Results

Clinical laboratory evaluations were not assessed in the booster portion of this study.

6.3.12.7 Dropouts and/or Discontinuations

For both age cohorts, no participants were withdrawn due to AEs from Dose 3 to the data cutoff date (November 3, 2022, for 12-17 years of age, November 22, 2021, for 18-55 years of age).

6.3.13 Study Summary and Conclusions

12-15 years of age:
A total of 825 participants 12-15 years of age received BNT162b2 (Original) 30μg Dose 3 after a 2-dose primary series of BNT162b2 (Original). The median time between Dose 2 and Dose 3 vaccination was 11.2 months (range: 6.3-20.1). The median duration of safety follow-up after Dose 3 was 9.5 months (range: 1.5 to 10.7 months); 86.9% had safety follow-up ≥6 months after BNT162b2 (Original), 30 μg Dose 3. No participants reported myocarditis or pericarditis. Review of AEs and SAEs following BNT162b2 (Original) Dose 3 did not identify any new safety concerns and supports the safety of single dose use in individuals 12-15 years of age who previously received BNT162b2 (Original) vaccine.

18-55 years of age:
A total of 306 participants 18-55 years of age received a BNT162b2 (Original), 30 μg Dose 3 after a 2-dose primary series of BNT162b2 (Original). The median time between Dose 2 and Dose 3 vaccination was 6.8 months (range: 4.8-8.0 months). More than 95% of the 306 participants 18 -55 years of age completed the 6-month safety follow-up visit after 30 μg BNT162b2 (Original) Dose 3. From the time of the BNT162b2 (Original) Dose 3 to the 1-month follow-up visit, 5.2% reported lymphadenopathy. Review of SAEs, and AESIs ≥6 months after BNT162b2 (Original), 30 μg Dose 3 did not identify any new safety concerns and supports the safety of single dose use in individuals 18-55 years of age who previously received BNT162b2 (Original) vaccine.

Taken, together, these data supported the safety for use of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older.

6.4 Study BNT162-17

NCT05004181
"A Phase 2 Trial to Evaluate the Safety and Immunogenicity of SARS-CoV-2 Monovalent and Multivalent RNA-based Vaccines in Healthy Subjects"

The Applicant provided re-analyses of immunogenicity data from study BNT162-17, which was intended to support the effectiveness of a single dose of Comirnaty in COVID-19 vaccine-naïve, baseline SARS-CoV-2 seropositive individuals ≥12 years of age. Study BNT162-17 consisted of three parts, of which some of the objectives in Part B were to evaluate the safety and immunogenicity of a bivalent BNT162b2 (alpha/delta variant) [i.e., BNT162b2 bivalent (B.1.1.7 + B.1.617.2)], 30 µg, vaccine administered to COVID-19 vaccine-naïve participants as two doses 21 days apart, without evidence of prior SARS-CoV-2 infection (Cohort 6). The immunogenicity at 21 days post-Dose 1 elicited by this variant vaccine was analyzed with validated assays to fill the evidence to support the use of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in individuals 12 years old and older who have not been previously vaccinated.

- Analyses of the primary endpoints were compared to demonstrate noninferiority of immune responses after one 30 µg dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve subjects with evidence of prior infection with the immune response after two doses of BNT162b2 (Original) in subjects without evidence of infection, age-matched adults from the study in which BNT162b2 (Original) efficacy was demonstrated (Study C4591001). Sera from the comparator group were tested contemporaneously with sera from Part B, Cohort 6 participants, with a validated CPE-based microneutralization assay using the SARS-CoV-2 reference strain (USA-WA1/2020).
- The secondary immunogenicity endpoints of variant-specific neutralizing titers (Alpha, Delta, Omicron BA.5) were evaluated descriptively following bivalent BNT162b2 (alpha/delta variant) Dose 1.
- Immune responses from Part B, which enrolled individuals 18-85 years of age, were extrapolated to individuals 12-17 years of age because the dose (30 µg) for individuals 12-17 years of age is the same as that for ≥18 years and older and there is no reason a priori to expect that immune responses following the same dosage would be lower in adolescents 12-17 years of age compared with adults ≥18 years of age.

Part A, C, and some of the Part B objectives pertained to immunogenicity evaluations of COVID-19 vaccine-experienced participants, and therefore are not covered in this review. Also, the safety evaluations are not presented in this review, since data from study BNT162-17 were intended by the Applicant only to address FDA's request to provide immunogenicity data to support the effectiveness of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in COVID-19 vaccine-naïve, baseline SARS-CoV-2 seropositive individuals ≥12 years of age.

6.4.1 Objectives

Primary Immunogenicity
To demonstrate the noninferiority of immune responses against the reference strain after BNT162b2 bivalent (B.1.1.7 + B.1.617.2) Dose 1 in COVID-19 vaccine-naïve participants with evidence of prior infection (seropositive), compared with Post-Dose 2 immune responses in Study C4591001 participants who were COVID-19 vaccine-naïve without evidence of SARS-CoV2 infection prior to Dose 1. [Cohort 6 vs. Study C4591001 comparator]

Primary Endpoints: GMT and seroresponse using the reference strain

Secondary Immunogenicity
To compare immune responses against variants of concern (VOCs) in participants vaccinated with BNT162b2 bivalent (B.1.1.7 + B.1.617.2) after

- Dose 1 in Cohort 6 participants who were COVID-19 vaccine naïve and had evidence of prior SARS-CoV-2 infection (seropositive), compared with
  - Dose 2 in Cohort 6 participants
  - Dose 3 in COVID-19 vaccine-experienced participants without evidence of prior SARS-CoV-2 infection (Cohort 1)

Secondary Endpoints: GMTs and seroresponse using Alpha (B.1.1.7), Delta (B.1.617.2) and Omicron BA.5 (B.1.1.529.5) strains

Reviewer Comment*: At the time that SARS-CoV-2 Delta variant emerged, a third dose of an RNA-based vaccine (Original strain) temporarily increased protection against severe COVID-19. Available real-world data now indicate that SARS-CoV-2 seropositive individuals respond adequately to a single dose of COVID-19 vaccine. The secondary objective was to describe immune responses after a single dose of BNT162b2 (Original) in a COVID-19 vaccine-naive participant with prior exposure to SARS-CoV-2 [Cohort 6 Dose 1] compared with immune responses in Cohort 6 individuals and Cohort 1 individuals with no evidence of prior SARS-CoV-2 infection and then vaccinated with >1 dose.*

6.4.2 Design Overview

In Part A, BNT162b2 bivalent (B.1.1.7 + B.1.617.2) was evaluated in BNT162b2 (Original)-experienced individuals and was administered as a 1-, 2-dose regimen or administered as separate monovalent components (Cohorts 1-4) vs. BNT162b2 (Original) (Cohort 5). Cohort 6 was comprised of COVID-19 vaccine-naive individuals who received 3 doses of BNT162b2 bivalent (B.1.1.7 + B.1.617.2).

In Part B, only enrollment in Cohorts 1, 4 and 6 from Part A (n=~20/per cohort) were expanded evaluate safety and immunogenicity in more participants. Each of the cohorts in Part B enrolled 300 participants (18-85 years of age).

- Cohort 6: COVID-19 vaccine-naïve seropositive participants who received 3 doses of BNT162b2 (Original), 30 µg BNT162b2 bivalent (B.1.1.7 + B.1.617.2), at Day 1, Day 21, and a third dose approximate 6 months after Dose 2.
- Cohort 1: participants who had previously received 2 doses of 30µg BNT162b2 (Original) with Dose 2 administered at least 6 months before enrollment in Study BNT162-17). In study BNT162-17, 1 dose of 30 µg BNT162b2 bivalent (B.1.1.7 + B.1.617.2) was administered on Day 1.

Reviewer Comment*: Participants in Cohort 4 Parts A and B received BNT162b2 (B.1.617.2) and eligible participants were COVID-19 vaccine-experienced individuals. This cohort is not described in subsequent sections since no data were provided for Cohort 4.*

6.4.3 Population

Part B: Summarized Inclusion Criteria: participants 18 to ≤85 years old. Cohort 6 participants were COVID-19 vaccine-naïve with no medical history of SARS-CoV-2 infection. For Cohort 1, participants in Study C4591001 who completed a BNT162b2 (Original) 2-dose primary series and had no medical history of SARS-CoV-2 infection were eligible for enrollment in study BNT162-17; at enrollment in study BNT162-17, their participation in Study C4591001 was terminated.

Part B: Summarized Exclusion Criteria: medical or psychiatric condition including recent (within past year) or immunocompromised condition or suspected immunodeficiency or were pregnant or breastfeeding. Individuals were also excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention, current or prior immunosuppressant medications, blood products, immunoglobin or monoclonal antibodies within 60 days of enrollment.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Part B:

- Cohort 6: 3 doses of 30 µg BNT162b2 bivalent (B.1.1.7 + B.1.617.2), Dose 1 and 2 on Day 1 and Day 21 respectively and Dose 3 ~6 months after Dose 2.
- Cohort 1: 1 dose of 30 µg BNT162b2 bivalent (B.1.1.7 + B.1.617.2), on Day 1
- Route of administration: IM

6.4.5 Directions for Use

Detailed instruction for vaccine preparation and administration are described in the full prescribing information in the Comirnaty PI.

6.4.6 Sites and Centers

This study was conducted at 11 sites in South Africa, 10 sites in the U.S., and 5 sites in Turkey.

6.4.7 Surveillance/Monitoring

Immunogenicity Monitoring: Blood samples were taken for immunogenicity assessments at Day 1, Day 8, Day 21, Day 29, Day 120, and Day 360. Additional blood samples were taken at early termination or any COVID-19 infection. Each of these samples were intended for serological testing for SARS-CoV-2 N-binding antibodies and for humoral immunogenicity.

The variant-specific neutralizing titers were based on validated assays for SARS-CoV-2 NT50 against SARS-CoV-2 variants Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron BA.5 (B.1.1.529.5) using clinical SARS-CoV-2 isolates in a cytopathic effect (CPE)-based microneutralization assay; all samples were tested contemporaneously.

6.4.8 Endpoints and Criteria for Study Success

See Section 6.4.9

6.4.9 Statistical Considerations & Statistical Analysis Plan

Primary Immunogenicity Sample

Approximately 275 participants enrolled in BNT162-17 Part B Cohort 6 had evidence of prior infection and were included in reference strain neutralization testing at baseline and 3 weeks post-Dose 1. The comparator group was a random subset of approximately 275 participants with matching sex and age selected from Study C4591001 participants who received 2 doses of BNT162b2 (Original) and had no evidence of infection up to 1-month post-Dose 2. Baseline and 1-month post-Dose 2 samples from the comparator group were tested contemporaneously with samples from Part B Cohort 6 participants.

Primary Immunogenicity Endpoints

The primary immunogenicity objectives were to assess:

- Noninferiority of the reference strain immune response at 3 weeks post-Dose 1 (hereafter referred to as “3W PD1”) of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior infection in Study BNT162-

17 Part B Cohort 6 to that at 1 month post-Dose 2 (hereafter referred to as "1M PD2") of BNT162b2 (Original) in participants without evidence of infection in Study C4591001 in terms of 1) GMT and 2) seroresponse rate.

- Noninferiority of reference strain immune response in terms of GMT was evaluated first, followed by seroresponse rate. GMT noninferiority was declared if the lower bound of the 2-sided 95% CI was greater than 0.67 for the GMT of reference strain NT at 3W PD1 of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in Cohort 6 divided by the GMT of reference strain NT at 1M PD2 of BNT162b2 (Original) in participants without evidence of infection in Study C4591001 (GMR). Seroresponse noninferiority was declared if the lower bounds of the 2-sided 95% CIs was greater than -10% for the difference in percentage SRR comparing the seroresponse at 3W PD1 of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in Cohort 6 to the seroresponse at 1M PD2 of BNT162b2 (Original) in participants without evidence of infection in Study C4591001.

Primary immunogenicity analyses were based on sera tested in validated assays for 50% SARS-CoV-2 neutralizing titers against the reference strain on a 384-well assay platform (reference strain [USA-WA1/2020, isolated in January 2020]).

Secondary Immunogenicity Sample

A Part B Cohort 6 subset of approximately 148 participants with evidence of prior infection were selected for variant-specific neutralization testing at baseline and 3 weeks after Dose 1. Approximately 148 participants enrolled in Part B Cohort 1 and 25 participants enrolled in Part B Cohort 6 who had negative SARS-CoV-2 N-binding antibody results at baseline and 1-month post-Dose 3 in Cohort 1 and post-Dose 2 in Cohort 6 visits were selected for variant-specific neutralization testing.

Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints of variant-specific neutralizing titers (Alpha, Delta, Omicron BA.5) were evaluated descriptively. Variant-specific immune responses were compared between selected participants in Part B Cohort 1 and Part B Cohort 6.

More specifically, immune responses at 3 weeks after *1 dose* (referred to as "3W PD1") of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior infection in Study BNT162-17 Part B Cohort 6 were compared with:

1) immune responses at 1 month after *2 doses* (referred to as "1M PD2") of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) as a primary series in COVID-19 vaccine-naïve participants (Cohort 6) without evidence of infection in Study BNT162-17; and,
2) immune responses at 1 month after 1 booster dose (3rd dose overall) with BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in BNT162b2 (Original)-experienced participants (Cohort 1) without evidence of infection in Study BNT162-17.

The variant-specific neutralizing titers were based on validated assays for 50% SARS-CoV-2 neutralizing titers against SARS-CoV-2 variants Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron BA.5 (B.1.1.529.5) using clinical SARS-CoV-2 isolates in a CPE-based microneutralization assay; all samples were tested contemporaneously.

Immunogenicity analyses

GMT, GMR

GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t-distribution). Model-based GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of least squares (LS) means

and corresponding CIs based on the analysis of logarithmically transformed neutralizing titers using a linear regression model with terms for age, sex, and group. For GMT calculations, titers below the LLOQ were set to 0.5 × LLOQ, and titers above the upper limit of quantification (ULOQ) were set to ULOQ.

Unadjusted GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers and the corresponding CIs (based on the Student t-distribution). A linear regression model with age, sex and group (each Part B cohort vs reference) as explanatory variables and natural log transformed antibody titers as dependent variable will be used to calculate the adjusted GMR and 2-sided 95% CI.

Seroresponse Rate
Seroresponse was defined as achieving a ≥4-fold rise from baseline. If the baseline measurement was below the LLOQ, a postvaccination assay result of ≥4 × LLOQ was considered a seroresponse. The exact 2-sided 95% CIs were based on the Clopper-Pearson method.

The adjusted difference in proportions was estimated using minimum risk weights and stratified by sex and age group (18-55 and 56-85 years of age), expressed as a percentage. The 2-sided 95% CI was calculated using Newcombe method stratified by sex and age group with minimum risk weights for the difference in proportions. The unadjusted difference in proportions was expressed as a percentage and the associated 2-sided 95% CI was based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

6.4.10 Study Population and Disposition – Primary Immunogenicity Analysis

6.4.10.1 Population Enrolled/Analyzed – Primary Immunogenicity Analysis

Reference (Original) Strain Immunogenicity Population
A total of 276 participants were in each of the 2 groups. The immunogenicity analysis set of BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group included 94.9% (n=262) and 99.6% (n=275) in C4591001 BNT162b2 (Original) group. Participants excluded from the immunogenicity analysis set for not having at least 1 valid and determinate immunogenicity result within the specified window after study vaccination included 5.1% (n=14) in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group and 0.4% (n=1) in the C4591001 BNT162b2 (Original) group. The 14 participants in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group had valid neutralization results but they were obtained outside the specified window, hence, these participants were included in the mITT set and excluded from the immunogenicity analysis set.

6.4.10.1.1 Demographics – Primary Analysis

Reference (Original) Strain Immunogenicity Population
The demographic characteristics of the immunogenicity analysis set are presented in Table 23. In the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group, 64.5% were Black or African American, 96.6% were from South Africa, and 97.3% were of non-Hispanic/non-Latino ethnicity. Participants received the study vaccination (Dose 1) from March to July 2022.

In the C4591001 BNT162b2 (Original) group, 83.6% were White, 70.5% were from the U.S., and 69.8% were of non-Hispanic/non-Latino ethnicity. Participants received study vaccination (Dose 2) from August to December 2020.

Other demographic characteristics, including sex and age at first vaccination, were balanced between the 2 groups, other than obesity for which 33.1% were obese in the C4591001 group compared to 24.8% in the BNT162-17 group.

Table 23. Demographic Characteristics, Reference Strain Neutralization, Immunogenicity Analysis Set, Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series)

Characteristic	Study BNT162-17 Cohort 6[a] N=262[c] n (%) or value (SD)[d]	Study C4591001[b] N=275 n (%) or value (SD)[d]
Sex	-	-
Male	109 (41.6)	113 (41.1)
Female	153 (58.4)	162 (58.9)
Race	-	-
White	4 (1.5)	230 (83.6)
Black or African American	169 (64.5)	25 (9.1)
American Indian or Alaska Native	0	2 (0.7)
Asian	0	7 (2.5)
Multiracial	37 (14.1)	7 (2.5)
Not reported	0	4 (1.5)
Other	52 (19.8)	0
Ethnicity	-	-
Hispanic/Latino	5 (1.9)	83 (30.2)
Non-Hispanic/non-Latino	255 (97.3)	192 (69.8)
Unknown	2 (0.8)	0
Country	-	-
Argentina	0	49 (17.8)
Brazil	0	19 (6.9)
Germany	0	3 (1.1)
South Africa	253 (96.6)	8 (2.9)
Turkey	0	2 (0.7)
U.S.	9 (3.4)	194 (70.5)
Age group (at first study vaccination)	-	-
18-55 Years	171 (65.3)	181 (65.8)
56-85 Years	91 (34.7)	94 (34.2)
18-64 Years	242 (92.4)	255 (92.7)
65-85 Years	20 (7.6)	20 (7.3)
Age at first study vaccination (years)	-	-
Mean (SD)	42.9 (16.2)[d]	42.7 (16.1)[d]
Median	41.0	40.0
Min, max	(18, 84)	(18, 84)
Age at screening (years)	-	-
Mean (SD)	42.9 (16.2)[d]	42.7 (16.1)[d]
Median	41.0	40.0
Min, max	(18, 84)	(18, 84)
Body mass index (BMI)	-	-
Underweight (<18.5 kg/m2)	27 (10.3)	2 (0.7)
Normal weight (≥18.5-<25.0 kg/m2)	110 (42.0)	108 (39.3)
Overweight (≥25.0-<30.0 kg/m2)	57 (21.8)	74 (26.9)
Obese (≥30.0 kg/m2)	65 (24.8)	91 (33.1)
Missing	3 (1.1)	0

Characteristic	Study BNT162-17 Cohort 6[a] N=262[c] n (%) or value (SD)[d]	Study C4591001[b] N=275 n (%) or value (SD)[d]
Height (cm)[c]	-	-
Mean (SD)	165.1 (9.1)[d]	169.4 (9.5)[d]
Median	165.0	169.0
Min, max	(139, 192)	(145, 193)
Weight (kg)	-	-
Mean (SD)	70.4 (19.1)	80.2 (21.0)
Median	66.3	76.3
Min, max	(34, 177)	(49, 168)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 3, p17-19
Notes:
a. Study BNT162-17 Cohort 6=BNT162b2 (B.1.1.7 + B.1.617.2) 30 µg with evidence of prior infection as shown by positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Study C4591001=BNT162b2 (Original) 30 µg without evidence of infection as determined by participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection) of SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result at the Dose 1 and 1-month post–Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit (up to the 1- month post–Dose 2 blood sample collection)) and had no medical history of COVID-19 were included in the analysis.
c. For Study BNT162-17 Cohort 6 group, the N=262 for all demographic characteristic except height where N=259, while for Study
d. Value (standard deviation [SD]) reported for age at first study vaccination (years), age at screening (years), height (cm), and weight (kg).
C4591001 group, N=275 for all characteristics
Abbreviations: N, number of participants in the specified group; n (%), number and percentage of participants with the specified characteristic; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.4.10.1.3 Subject Disposition

Not applicable.

6.4.11 Efficacy Analyses – Primary Immunogenicity Endpoints

6.4.11.1 Analyses of Primary Endpoint(s)

Geometric Mean Ratio: *Reference Strain Neutralization*

In the immunogenicity analysis set, model-based GMR of reference strain neutralizing titer in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group at 3W PD1 to that in the C4591001 BNT162b2 (Original) group at 1M PD2 was 13.12 (95% CI: 11.14, 15.45) (Table 24). Noninferiority of reference strain immune response in terms of GMT for the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group was met, as the model-based LB of the 2-sided 95% CI for GMR was >0.67; the reference strain neutralizing titers were statistically significantly higher in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group than those in the C4591001 BNT162b2 (Original) group. The prevaccination reference strain neutralization GMT was substantially higher in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group compared with the C4591001 BNT162b2 (Original) group (GMT 813.1 vs 44.5, respectively), which was expected given that participants in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group had prior SARS-CoV-2 infection.

Table 24. Geometric Mean Ratio, Reference Strain Neutralization, Immunogenicity Analysis Set, Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series)

SARS-CoV-2 neutralization assay-NT50	Study BNT162-17 Cohort 6 (With Evidence of Prior Infection[a]) N=262 GMT[c] (95% CI[c])	Study C4591001 (Without Evidence of Infection[b]) N=275 GMT[c] (95% CI[c])	Study BNT162-17 Cohort 6/ Study C4591001 GMR[d] (95% CI[d])
Reference (original) strain	17404.2 (15485.1, 19561.1)	1328.1 (1183.1, 1491.0)	13.12 (11.14, 15.45)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 4, p21.
Notes:
a. Study BNT162-17 Part B Cohort 6 = BNT162b2 bivalent (B.1.1.7 + B.1.617.2) 30 µg, evidence of prior infection determined by positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Study C4591001 = BNT162b2 (Original) 30 µg evidence of no prior infection determined by no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection) of SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the Dose 1 and 1-month post–Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit (up to the 1- month post–Dose 2 blood sample collection)) and had no medical history of COVID-19 were included in the analysis.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t-distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on the analysis of logarithmically transformed neutralizing titers using a linear regression model with terms of age, sex, and group. Assay results below the LLOQ were set to 0.5 × LLOQ.
Abbreviations: n (%), number and percentage of participants with valid and determinate assay results for the specified assay at the given sampling time point; GMR, geometric mean ratio; GMT, geometric mean titer; LLOQ, lower limit of quantitation; LS, least-squares; N-binding, SARS-CoV-2 nucleoprotein– binding; NAAT, nucleic acid amplification test; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Difference in Seroresponse: *Reference Strain Neutralization*
In the immunogenicity analysis set, 85.8% in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group at 3W PD1 and 90.5% in the C4591001 BNT162b2 (Original) group at 1M PD2 achieved a seroresponse to the reference strain (Table 25). The adjusted difference in percentages of participants in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group at 3W PD1 compared with the participants with seroresponse in the C4591001 BNT162b2 (Original) group at 1M PD2 was -4.55% (95% CI: -10.04, 0.83). Noninferiority of reference strain seroresponse rate for the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group was slightly missed, as the LB of the 2-sided 95% CI for the percentage difference in seroresponse rate for reference strain was 0.04% lower than the noninferiority margin of -10%. Of note, the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group had higher pre-vaccination titers than the C4591001 BNT162b2 (Original) group due to prior SARS-CoV-2 infection, which makes achieving seroresponse a higher hurdle as fold rise is dependent upon the baseline titer. In addition, participants in the C4591001 BNT162b2 (Original) group had a longer time (1M PD2) than those in the BNT162b2 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) (3W PD1) to mount an immune response.

Unadjusted difference in percentage of participants with seroresponse between the two groups in the immunogenicity analysis set was similar to the adjusted difference. The unadjusted difference in reference strain percentage seroresponse rates between the two groups in the mITT set was -4.46 (95% CI -9.98, 0.94), with the LB of the 2-sided 95% CI above the -10% noninferiority margin.

The 14 participants in the mITT set who were excluded from the immunogenicity analysis set had immunogenicity blood samples drawn outside the specified window (Day 7 for 1 participant and ranging from Day 27-57 for the remaining 13 participants). The blood draw timepoint for participants in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group was 3W PD1,

whereas the corresponding timepoint for the C4591001 BNT162b2 (Original) group was 1M PD2.

Table 25. Percentage Difference, Participants with Seroresponse, Reference Strain Neutralization, Immunogenicity Analysis Set, Study BNT162-17 Part B Cohort 6 (Primary Series) and Subset of Study C4591001 (Primary Series)

SARS-CoV-2 Neutralization Assay – NT50	Study BNT162-17 Cohort 6 With Evidence of Prior Infection[a] N[c]=260 % (n)[d] (95% CI[e])	Study C4591001 Without Evidence of Infection[b] N[c]=275 % n[d] (95% CI[e])	Study BNT162-17 Cohort 6/ Study C4591001 Difference %[f] (95% CI[g])
Reference (original) strain	85.5 (223) (80.9, 89.8)	90.5 (249) (86.5, 93.7)	-4.55 (-10.04, 0.83)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 5, p23.
Notes: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. Study BNT162-17 Part B Cohort 6 = BNT162b2 bivalent (B.1.1.7 + B.1.617.2) 30 µg, evidence of prior infection determined by positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination. Protocol-specified timing for blood sample collection: 3W PD1 – Cohort 6 with evidence of prior infection; 1M PD2 – BNT162b2 (Original) 30 µg without evidence of infection.
b. Study C4591001 = BNT162b2 (Original) 30 µg evidence of no prior infection determined by no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection) of SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the Dose 1 and 1-month post–Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit (up to the 1- month post–Dose 2 blood sample collection)) and had no medical history of COVID-19 were included in the analysis.
c. Participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection) of SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the Dose 1 and 1-month post–Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit (up to the 1-month post–Dose 2 blood sample collection)) and had no medical history of COVID-19 were included in the analysis.
d. N=number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
e. n=Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.
g. Adjusted difference in proportions estimated using minimum risk weights and stratified by sex and age group (18-55 years, 56-85 years), expressed as a percentage.
Abbreviations: LLOQ, lower limit of quantitation; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Reviewer Comment*: It is important to note that there was higher baseline GMT for the seropositive individuals and a shorter time before collection of the follow-up titer (3 weeks vs. 4 weeks). The study met immunobridging criteria for GMR for the reference strain and just missed immunobridging criteria for percentage seroresponse for the reference strain (LB of 95% CI was -10.04% which is below the prespecified criteria of -10%). This near miss could be partially due to the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group having higher prevaccination titers than the C4591001 BNT162b2 (Original) group due to prior SARS-CoV-2 infection which makes achieving seroresponse criteria more challenging. It could also be related to participants in the C4591001 BNT162b2 (Original) group having had a longer time (1M PD2) than those in the BNT162-17 BNT162b2 bivalent (B.1.1.7 + B.1.617.2) group (3W PD1) to mount an immune response.*

6.4.12 Study Population and Disposition – Secondary Immunogenicity Analysis

6.4.12.1 Population Enrolled/Analyzed – Secondary Immunogenicity Analysis

Variant (Alpha, Delta, and Omicron BA.5) Strain Immunogenicity Population

Variant neutralization data were summarized for the subset of 149 participants in Part B Cohort 6 with evidence of prior infection (as of the cutoff date of October 06, 2022,) (hereafter

referred to as Cohort 6 with evidence of prior infection group). Comparator subsets of 19 participants from Part B Cohort 6 without evidence of infection (as of the cutoff date of October 06, 2022) (hereafter referred to as Cohort 6 without evidence of infection group) and 136 participants from Part B Cohort 1 without evidence of infection group (as of the cutoff date of April 08, 2022) (hereafter referred to as Cohort 1 without evidence of infection group) were also presented. A few participants preselected for variant neutralization testing in the 2 comparator groups were later identified as not meeting without evidence of infection definition due to positive or missing NAAT results or COVID-19 AE; these participants were not included in the summary for this report.

A total of 149, 19, and 136 participants were in each of the 3 groups (Table 26). The immunogenicity analysis set included 95.3%(n=142) in the Cohort 6 with evidence of prior infection group, 89.5% (n=17) in the Cohort 6 without evidence of infection group, and 100.0% (n=136) in the Cohort 1 without evidence of infection group. Overall, 4.7% (n=7) in the Cohort 6 with evidence of prior infection group and 10.5% (n=2) in the Cohort 6 without evidence of infection group were excluded from the immunogenicity analysis set for not having at least 1 valid and determinate immunogenicity result within the specified window after study vaccination. No participant in Cohort 1 without evidence of infection group was excluded from the immunogenicity analysis set.

Table 26. Participant Disposition, Immunogenicity Populations, Variant Neutralization Receiving BNT162b2 bivalent (B.1.1.7 + B.1.617.2) 30 µg, Study BNT162-17, Subset of Part B Cohort 6 (Primary Series) and Study BNT162-17, Cohort 1 (Booster)

Participant Disposition	Cohort 6 With Evidence of Prior Infection[a] n (%)	Cohort 6: Without Evidence of Prior Infection[b] n (%)	Cohort 1: Without Evidence of Prior Infection[b] n (%)
Assigned: N	149 (100)	19 (100)	136 (100)
All-available immunogenicity set (mITT)	149 (100)	19 (100)	136 (100)
Excluded from all-available immunogenicity set (mITT)	0	0	0
Immunogenicity analysis set	142 (95.3)	17 (89.5)	136 (100)
Excluded from immunogenicity analysis set	7 (4.7)	2 (10.5)	0
Reason for exclusion[c]	-	-	-
Did not have at least 1 valid and determinate immunogenicity result within the specified window[d] at the reporting time point[e]	7 (4.7)	2 (10.5)	0

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 9, p35-36.
Notes: a. Positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and up to the 1-month post–study vaccination blood sample collection for Cohort 1) of SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result and negative NAAT [oral swab] at all planned visits and any unscheduled visit (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1)) and had no

medical history or adverse event of COVID-19 (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1) were included in the analysis.
c. Participants may have been excluded for more than 1 reason.
d. Specified windows for blood sample collection at the reporting time point: 3W PD1: ≥16 to ≤26 days after Dose 1 – Cohort 6 with evidence of prior infection; 1M PD2: ≥19 to ≤39 days after Dose 2 – Cohort 6 without evidence of infection; 1M PD1: ≥19 to ≤39 days after the study vaccination – Cohort 1 without evidence of infection.
e. Immunogenicity analysis set windows for blood sample collection: 3W PD1 – Cohort 6 with evidence of prior infection; 1M PD2 – Cohort 6 without evidence of infection; 1M PD1 – Cohort 1 without evidence of infection.
Abbreviations: N,number of participants in the group; n, number of participants with the specified characteristic; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

6.4.12.1.1 Demographics

Variant (Alpha, Delta, and Omicron BA.5) Strain Immunogenicity Population

Most demographic characteristics were imbalanced between the cohorts, while demographic characteristics for participants in mITT set were similar to those in the immunogenicity analysis set.

Table 27. Demographic Characteristics, Variant Neutralization, Immunogenicity Analysis Set, Study BNT162-17, Cohort 6, Subset of Part B (Primary Series) and Cohort 1 (Booster)

Characteristic	Cohort 6 With Evidence of Prior Infection[a] N=142 n (%) or value (SD)[e]	Cohort 6 Without Evidence of Prior Infection[b] N=17 n (%) or value (SD)[e]	Cohort 1 Without Evidence of Prior Infection[b] N=136 n (%) or value (SD)[e]
Sex	-	-	-
Male	68 (47.9)	11 (64.7)	75 (55.1)
Female	74 (52.1)	6 (35.3)	61 (44.9)
Race	-	-	-
White	1 (0.7)	4 (23.5)	114 (83.8)
Black or African American	96 (67.6)	9 (52.9)	7 (5.1)
American Indian or Alaska Native	0	0	1 (0.7)
Asian	0	0	5 (3.7)
Multiracial	21 (14.8)	1 (5.9)	9 (6.6)
Other	24 (16.9)	3 (17.6)	0
Ethnicity	-	-	-
Hispanic/Latino	3 (2.1)	3 (17.6)	15 (11.0)
Non-Hispanic/non-Latino	138 (97.2)	14 (82.4)	120 (88.2)
Not reported	0	0	1 (0.7)
Unknown	1 (0.7)	0	0
Country	-	-	-
South Africa	137 (96.5)	9 (52.9)	19 (14.0)
Turkey	0	0	49 (36.0)
U.S.	5 (3.5)	8 (47.1)	68 (50.0)
Age group (at first study vaccination)	-	-	-
18-55 Years	92 (64.8)	5 (29.4)	87 (64.0)
56-85 Years	50 (35.2)	12 (70.6)	49 (36.0)
18-64 Years	130 (91.5)	14 (82.4)	115 (84.6)
65-85 Years	12 (8.5)	3 (17.6)	21 (15.4)
Age at first study vaccination (years)	-	-	-
Mean (SD)	42.3 (16.7)[e]	55.2 (13.9)[e]	47.6 (15.4)[e]
Median	38.5	59.0	49.0
Min, max	(18, 79)	(24, 78)	(18, 80)

Characteristic	Cohort 6 With Evidence of Prior Infection[a] N=142 n (%) or value (SD)[e]	Cohort 6 Without Evidence of Prior Infection[b] N=17 n (%) or value (SD)[e]	Cohort 1 Without Evidence of Prior Infection[b] N=136 n (%) or value (SD)[e]
Age at screening (years)	-	-	-
Mean (SD)	42.3 (16.7)[e]	55.2 (13.9)[e]	47.6 (15.4)[e]
Median	38.5	59.0	49.0
Min, max	(18, 79)	(24, 78)	(18, 80)
Time from Dose 2 of BNT162b2 (Original)[c] (received prior to the study) to the first study vaccination (months[d])	-	-	-
n	N/A	N/A	136
Mean (SD)	-	-	10.4 (1.9)[e]
Median	-	-	10.2
Min, max	-	-	(6.7, 15.4)
≥6 to <9 Months	-	-	35 (25.7)
≥9 to ≤12 Months	-	-	60 (44.1)
>12 Months	-	-	41 (30.1)
Time from Dose 2 of BNT162b2 (Original)[c] (received prior to the study) to the first study vaccination (days)	-	-	-
n	N/A	N/A	136
Mean (SD)	-	-	317.9 (57.2)[e]
Median	-	-	309.0
Min, max	-	-	(203, 470)
Body mass index (BMI)	-	-	-
Underweight (<18.5 kg/m2)	11 (7.7)	2 (11.8)	3 (2.2)
Normal weight (≥18.5-<25.0 kg/m2)	67 (47.2)	9 (52.9)	41 (30.1)
Overweight (≥25.0-<30.0 kg/m2)	33 (23.2)	4 (23.5)	41 (30.1)
Obese (≥30.0 kg/m2)	31 (21.8)	2 (11.8)	48 (35.3)
Missing	0	0	3 (2.2)
Height (cm)	-	-	-
n	142	17	133
Mean (SD)	165.5 (9.71)	168.4 (9.30)	170.6 (8.6)[e]
Median	167.0	170.2	170.0
Min, max	(139, 192)	(156, 188)	(152, 189)
Weight (kg)	-	-	-
n	142	17	136
Mean (SD)	69.5 (18.17)	69.9 (23.46)	83.1 (21.5)[e]
Median	66.0	62.9	80.0
Min, max	(34, 177)	(42, 136)	(47, 154)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 10, p38-41.
Notes:
a. Positive N-binding ant body result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and up to the 1-month post–study vaccination blood sample collection for Cohort 1) of SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result and negative NAAT [oral swab] at all planned visits and any unscheduled visit (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1)) and had no

medical history or adverse event of COVID-19 (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1) were included in the analysis.
c. For one subject this is calculated as the time from Dose 2 of an unspecified COVID-19 vaccine (received prior to the study) to the first study vaccination.
d. Month was calculated as 30.4375 days.
e. Value (standard deviation [SD]) reported for age at first study vaccination (years), age at screening (years), height (cm), and weight (kg).
Abbreviations: N, number of participants in the specified group; n (%), number and percentage of participants with the specified characteristic; N/A, not applicable; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Reviewer Comment: *There are imbalances between the studies and cohorts in terms of all demographics. Study BNT162-17, particularly Cohort 6 With Evidence of Prior Infection is largely Black/African American (>60%), largely from South Africa (>96%), and few Hispanic participants (2%) compared to 1) C4591001 – 9% Black, 3% from South Africa/ >70% from U.S., and 30% Hispanic, 2) Cohort 6: Without Evidence of Prior Infection - 53% Black, 53% from South Africa, 18% Hispanic, and 3) Cohort 1: Without Evidence of Prior Infection – 5% Black, 14% from South Africa, and 11% Hispanic.*

6.4.12.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.4.12.1.3 Subject Disposition

Not applicable.

6.4.13 Efficacy Analyses – Secondary Immunogenicity Endpoints

6.4.13.1 Analyses of Secondary Immunogenicity Endpoints

Geometric Mean Ratio: *Variant (Alpha, Delta, and Omicron BA.5) Neutralization*
In the immunogenicity analysis set, the observed GMTs of Alpha, Delta, and Omicron BA.5 neutralizing titers at 3 weeks after a single dose in Cohort 6 vaccine-naïve participants with evidence of prior infection were numerically higher than at 1 month after 2 doses in Cohort 6 vaccine-naïve participants without evidence of infection and at 1 month after the third dose in Cohort 1 vaccine-experienced participants without evidence of infection (Table 28). The LB of the 2-sided 95% CI for model-based GMRs was >1 for all comparisons. Unadjusted GMRs in the immunogenicity analysis set and mITT set were similar to those in the immunogenicity analysis set.

Table 28. Geometric Mean Ratios, Variant Neutralization, Immunogenicity Analysis Set, Study BNT162-17 Subset of Part B Cohort 6 (Primary Series) and Cohort 1 (Booster)

SARS-CoV-2 Neutralization Assay - NT50	Cohort 6 With Evidence of Prior Infection 3W PD1[a] n=142[c] GMT[d] (95% CI[d])	Cohort 6 Without Evidence of Infection 1M PD2[b] n=17[c] GMT[d] (95% CI[d])	Cohort 1 Without Evidence of Infection 1M PD3[b] n=136[c] GMT[d] (95% CI[d])	Cohort 6 With Evidence of Prior Infection[a]/ Cohort 6 Without Evidence of Infection[b] GMR[e] (95% CI[e])	Cohort 6 With Evidence of Prior Infection[a]/ Cohort 1 Without Evidence of Infection[b] GMR[e] (95% CI[e])
Alpha (B.1.1.7)	1045.3 (853.1, 1280.8)	180.8 (91.8, 356.3)	749.5 (621.1, 904.6)	7.66 (4.09, 14.33)	1.46 (1.10, 1.93)
Delta (B.1.617.2)	859.9 (693.4, 1066.4)	62.6 (30.9, 127.0)	466.6 (401.8, 541.9)	15.43 (7.87, 30.28)	1.99 (1.44, 2.45)

SARS-CoV-2 Neutralization Assay - NT50	Cohort 6 With Evidence of Prior Infection 3W PD1[a] n=142[c] GMT[d] (95% CI[d])	Cohort 6 Without Evidence of Infection 1M PD2[b] n=17[c] GMT[d] (95% CI[d])	Cohort 1 Without Evidence of Infection 1M PD3[b] n=136[c] GMT[d] (95% CI[d])	Cohort 6 With Evidence of Prior Infection[a]/ Cohort 6 Without Evidence of Infection[b] GMR[e] (95% CI[e])	Cohort 6 With Evidence of Prior Infection[a]/ Cohort 1 Without Evidence of Infection[b] GMR[e] (95% CI[e])
Omicron BA.5 (B.1.1.529.5)	229.3 (191.7, 274.4)	10.2 (5.7, 18.3)	80.8 (66.9, 97.6)	29.86 (17.31, 51.49)	2.94 (2.26, 3.82)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 11, p43-44.
Notes: a. Protocol-specified timing for blood sample collection: 3W PD1 – 3 weeks after 1st dose for Cohort 6 with evidence of prior infection; 1M PD2 – 1 month after 2nd dose for Cohort 6 without evidence of infection; 1M PD3 – 1 month after Dose 3 (booster dose) for Cohort 1 without evidence of infection.
b. Positive N-binding ant body result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
c. Participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and up to the 1-month post–study vaccination blood sample collection for Cohort 1) of SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result and negative NAAT [oral swab] at all planned visits and any unscheduled visit (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1)) and had no medical history or adverse event of COVID-19 (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1) were included in the analysis.
d. n=Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
e. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t-distribution). Assay results below the LLOQ were set to 0.5 × LLOQ; assay results above the ULOQ were set to ULOQ.
f. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of the LS means and corresponding CIs based on the analysis of logarithmically transformed neutralizing titers using a linear regression model with terms of age, sex, and group. A separate model was fit for each comparison. Assay results below the LLOQ were set to 0.5 × LLOQ; assay results above the ULOQ were set to ULOQ.
Abbreviations: GMR, geometric mean ratio; GMT, geometric mean titer; LLOQ, lower limit of quantitation; LS, least-squares; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULOQ, upper limit of quantitation.

Percentage Difference in Seroresponse: *Variant (Alpha, Delta, and Omicron BA.5) Neutralization*

In the immunogenicity analysis set, the observed percentage seroresponse rates against Alpha, Delta, and Omicron BA.5 at 3 weeks after a single dose of vaccine in Cohort 6 vaccine-naïve participants with evidence of prior infection were high (>87%) (Table 29). Comparing with Cohort 6 without evidence of infection group at 1M PD2, there is a trend of higher seroresponse rates in Cohort 6 with evidence of prior infection group to Delta and, more prominently, to Omicron BA.5. Comparing with Cohort 1 without evidence of infection group at 1-month post-Dose 3 (1M PD3), the observed seroresponse rates in Cohort 6 with evidence of prior infection group were lower for Alpha and Delta and similar for Omicron BA.5. Unadjusted differences in percentage seroresponse rates in participants in the immunogenicity analysis set and in the mITT set were similar to those in the immunogenicity analysis set.

Table 29. Adjusted Percentage Difference, Participants with Seroresponse, Variant Neutralization, Immunogenicity Analysis Set, Study BNT162-17, Subset of Part B Cohort 6 (Primary Series) and Cohort 1 (Booster)

SARS-CoV-2 Neutralization Assay-NT50	Cohort 6 With Evidence of Prior Infection[a] 3W PD1 N=142[c] % (n)[d] (95% CI[e])	Cohort 6 Without Evidence of Infection[b] 1M PD2 N=17[c] % (n)[d] (%) (95% CI[e])	Cohort 1 Without Evidence of Infection[b] 1M PD1 N=136[c] % (n)[d] (95% CI[e])	Cohort 6 With Evidence of Prior Infection[a] Minus Cohort 6 Without Evidence of Infection[b] Difference %[f] (95% CI[g])	Cohort 6 With Evidence of Prior Infection[a] Minus Cohort 1 Without Evidence of Infection[b] Difference %[f] (95% CI[g])
Alpha (B.1.1.7)	87.3 (124) (80.7, 92.3)	76.5 (13) (50.1, 93.2)	97.1 (132) (92.6, 99.2)	7.0 (-9.7, 32.2)	-9.8 (-16.4, -3.2)
Delta (B.1.617.2)	89.4 (127) (83.2, 94.0)	58.8 (10) (32.9, 81.6)	96.3 (131) (91.6, 98.8)	20.9 (-0.6, 46.5)	-6.7 (-13.0, -0.4)
Omicron BA.5 (B.1.1.529.5)	87.3 (124) (80.7, 92.3)	11.8 (2) (1.5, 36.4)	80.1 (109) (72.4, 86.5)	81.5 (54.3, 90.1)	6.7 (-2.1, 15.4)

Source: Adapted from: STN125742/276.25 bnt162-17-single-dose-immuno-data.pdf Table 12, p46-47.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
Assay results below the LLOQ were set to 0.5 × LLOQ; assay results above the ULOQ were set to ULOQ.
a. Protocol-specified timing for blood sample collection: 3W PD1 – Cohort 6 with evidence of prior infection; 1M PD2 – Cohort 6 without evidence of infection; 1M PD1 – Cohort 1 without evidence of infection.
b. Positive N-binding ant body result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
c. Participants who had no serological or virological evidence (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and up to the 1-month post–study vaccination blood sample collection for Cohort 1) of SARS-CoV-2 infection (ie, negative N-binding antibody [serum] result and negative NAAT [oral swab] at all planned visits and any unscheduled visit (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1)) and had no medical history or adverse event of COVID-19 (up to the 1-month post–Dose 2 blood sample collection for Cohort 6 and 1-month post–study vaccination blood sample collection for Cohort 1) were included in the analysis.
d. N=number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
e. n=Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.
g. Adjusted difference in proportions estimated using minimum risk weights and stratified by sex and age group (18-55 years, 56-85 years), expressed as a percentage.
h. 2-Sided CI based on the Newcombe method stratified by sex and age group (18-55 years, 56-85 years) with minimum risk weights for the difference in proportions.
Abbreviations: LLOQ, lower limit of quantitation; N-binding, SARS-CoV-2 nucleoprotein–binding; NAAT, nucleic acid amplification test; NT50, 50% neutralizing titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULOQ, upper limit of quantitation.

Reviewer Comment*: In the evaluation of study BNT162-17 Cohorts 1 and 6, the immune response pattern to other variants (Alpha, Delta, and Omicron) was similar. GMTs were highest at baseline for the seropositive individuals from Cohort 6 with evidence of prior infection compared with Cohort 6 individuals and Cohort 1 individuals with no evidence of prior infection, but seroresponse rates were higher in individuals from Cohort 6 and Cohort 1 with no evidence of prior infection except for seroresponse rates to Omicron. All groups had the lowest seroresponse rates for Omicron – which likely reflects that the vaccine contained only Alpha and Delta variants. With specific regard to Omicron response, the highest seroresponse rate and post-dose GMT were in individuals in Cohort 6 with evidence of prior infection (vaccine-naïve seropositive), which could reflect Omicron exposure through natural infection, but it may also suggest hybrid immunity may induce numerically higher immune response. GMRs met noninferiority criteria for the baseline seropositive individuals from Cohort 6 compared with Cohort 6 individuals and Cohort 1 individuals with no evidence of prior infection. The difference*

in percentage seroresponse met noninferiority criteria for Cohort 6 individuals with evidence of prior infection compared with Cohort 6 compared with Cohort 6 individuals with no evidence of prior infection but not compared with Cohort 1 individuals with no evidence of prior infection (other than for Omicron). The dose for individuals 12-17 years of age is the same as that for ≥18 years of age; it is reasonable to extrapolate the vaccine effectiveness from the immune responses observed in ≥18 years old to 12-17 year olds when using the same dose.

6.4.14 Subpopulation Analyses

Subgroup analyses by age and by BMI showed a similar trend for GMT and seroresponse (DNS).

6.4.15 Study Summary and Conclusions

Analysis of immunogenicity data from COVID-19 vaccine-naïve participants 18-85 years of age who had evidence of prior SARS-CoV-2 infection after a single 30 µg dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2), encoding spike antigens for the Alpha and Delta SARS-CoV-2 variants, showed immune responses against the reference strain and Alpha, Delta and Omicron BA.5 variants. Although the Alpha (B.1.1.7) and Delta (B.1.617.2) variants are no longer epidemiologically relevant, experience with variant-modified versions of BNT162b2 is relevant because all have the same LNP formulation and RNA components except that the RNAs differ slightly in their encoded open reading frame, and the available data have demonstrated that immune response trends are similar. These data support the safety and effectiveness of a single dose (30 µg) of COMIRNATY including Comirnaty (2023-2024 Formula) in unvaccinated individuals 12 years of age and older. Data on effectiveness of a single dose (30 µg) in COVID-19 vaccine-naïve adults can be extrapolated to support the effectiveness of a single dose (30 µg) in COVID-19 vaccine-naïve adolescents due to the comparable efficacy and immunogenicity results observed after a 2-dose series of Comirnaty (Original monovalent) between adolescent participants and adult participants in Study BNT162-17 (see Section 6.4 of the Comirnaty BLA memorandum). Taken together, these data provide evidence to support the use of COMIRNATY, including Comirnaty (2023-2024 Formula), as a single dose in individuals 12 years of age and older, irrespective of previous COVID-19 vaccination status.

Reference Strain Neutralization

Comparison of the reference strain immune response in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection at 3 weeks after a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) with that at 1 month after 2 doses of the BNT162b2 (Original) in participants without evidence of prior infection in Study C4591001 was performed for immunobridging of the efficacy, as originally demonstrated in that study. Despite BNT162b2 bivalent (B.1.1.7 + B.1.617.2) not encoding the reference strain, this analysis demonstrated that a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection could be expected to have at least noninferior efficacy to 2 doses of BNT162b2 (Original) in participants without evidence of prior infection based upon:

- Noninferiority of the reference strain immune response based on GMR was met. Furthermore, the GMT was numerically higher at 3 weeks after the single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in participants with evidence of prior infection than at 1 month after 2 doses of BNT162b2 (Original) in participants without evidence of prior infection.
- Noninferiority of reference strain immune response by percentage difference in seroresponse rates was almost met, missing the noninferiority margin by 0.04%, which might be expected that a ≥ 4-fold increase in post-vaccination titer compared to pre-vaccination titer would be more difficult to achieve in participants with higher pre-

vaccination titer due to prior SARS-CoV-2 infection than pre-vaccination titers participants without evidence prior SARS-CoV-2 infection.

Variant Neutralization
Comparing the variant-specific immune responses among selected participants in Part B Cohort 6 and Part B Cohort 1:

- Descriptive analyses showed higher GMTs for Alpha, Delta, and Omicron BA.5 at 3 weeks after a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2), with the lower bound of 95% CI for GMR >1 for all comparisons, and
- High seroresponse rates to Alpha, Delta, and Omicron BA.5 were observed at 3 weeks after a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2).

BNT162-17 study vaccination (Dose 1) was performed from March to July 2022, and it is likely that many of the seropositive participants' exposure was due to an Omicron sublineage (BA.1, BA.2, BA.4, BA.5). Therefore, despite BNT162b2 bivalent (B.1.1.7 + B.1.617.2) encoding variants that are somewhat distant from Omicron BA.5, the most contemporaneous one evaluated in this study, the vaccine's immunogenicity against this variant, is reassuring.

Reviewer Comment: *The immunogenicity results suggest that a single dose of a more closely matched vaccine (e.g., encoding XBB.1.5) in seropositive COVID-19 vaccine-naïve individuals may perform at least as well against the matched strain.*

In the context of the Applicant's intended single dose use COMIRNATY including Comirnaty (2023-2024 Formula) for COVID-19 vaccine naïve seropositive individuals ≥12 years of age, SARS-CoV-2 neutralizing antibody responses from study BNT162-17 participants 18-85 years of age were extrapolated to individuals 12- <18 years of age, since COMIRNATY including Comirnaty (2023-2024 Formula) dose (30 µg) in individuals 12-17 years of age and ≥18 years of age is the same, and immune responses in individuals 12-17 years of age generally would not be expected to be lower than immune responses in adults.

This study enrolled participants in the first half of 2022, during a period when the Omicron variant emerged and became predominant, and the vaccine product that was evaluated was composed of Alpha and Delta variants. These data provide a proof of concept to support the conclusion that a single dose of the Pfizer-BioNTech COVID-19 Vaccine should be effective against COVID-19 regardless of previous vaccine experience. However, the generalizability of the conclusions is limited by imbalances in demographics between comparator groups and a poor match of demographics with a U.S. population. Due to limitations of this study, the Applicant committed to conduct Study C4591054, Substudy B as a postmarketing commitment (PMC) to provide substantial evidence of vaccine efficacy of a single dose of the COMIRNATY including Comirnaty (2023-2024 Formula) regardless of prior vaccination status in individuals ≥12 years of age.

7. INTEGRATED OVERVIEW OF EFFICACY

Immunogenicity of Comirnaty administered as a simplified regimen (single dose) was based on three studies (Studies C4591044, C4591001, and BNT162-17). An integrated summary of efficacy would not be informative because the study designs differed by vaccine administered [i.e., BNT162b2 (Original), BNT162b2 Bivalent (Original and Omicron BA.4/BA.5), or BNT162b2 bivalent (B.1.1.7 + B.1.617.2)], age, or geographic location. The totality of data on effectiveness supports the use of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status.

8. INTEGRATED OVERVIEW OF SAFETY

Safety of Comirnaty administered as a simplified regimen (single dose) was based on four studies (Studies C4591031, C4591044, C4591001, and BNT162-17). An integrated summary of safety would not be informative because the study designs differed by vaccine administered [i.e., BNT162b2 (Original), BNT162b2 Bivalent (Original and Omicron BA.4/BA.5), or BNT162b2 bivalent (B.1.1.7 + B.1.617.2)], age, or geographic location. The totality of data on safety supports the use of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

At the time of data cutoff date (February 8, 2022) of Study C4591031 Substudy A, exposure during pregnancy, defined as exposure within 28 days after last dose of study intervention, was reported by 4 participants (1 who received BNT162b2 (Original), and 3 who originally received placebo and then received BNT162b2 (Original) after unblinding). Two of the 4 participants, (1 placebo, 1 BNT162b2 (Original)) had a spontaneous abortion that was reported during the blinded follow-up period. The Applicant did not collect information about live birth outcomes, unknown pregnancy outcomes or ongoing pregnancies. In Study C4591001, no pregnancies were reported in the Phase 3 BNT162b2 (Original) booster group from Dose 3 to the data cutoff date (November 22, 2021.) No data on pregnancy or pregnancy outcomes were provided for Studies BNT162-17, C4591044, and C4591031 Substudy C.

There are two ongoing studies in pregnant individuals: Study C4591022, a registry study to assess pregnancy and infant outcomes after exposure to BNT162b2 (Original) during pregnancy in individuals ≥18 years of age in the U.S. and Canada; Study C4591015 is a randomized controlled trial in pregnant women in the U.S., Brazil, South Africa, and Europe.

9.1.2 Use During Lactation

It is not known if COMIRNATY is secreted in human breast milk. Data are not available to assess the effects of COMIRNATY on the breastfed infant or on milk production.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

For the age group 0 to <6 months, the pediatric study requirement was waived because evidence from Study C4591007 strongly suggests that a single dose of COMIRNATY would be ineffective in this age group. For age group 6 months to <12 years, submission of reports for Study C4591048, Substudies A and E, were deferred for this sBLA because the vaccine is ready for approval for use in individuals ≥12 years of age and the pediatric studies have not been completed.

The pediatric assessment in individuals 12 to <17 years of age was based on three studies. For individuals previously vaccinated with a COVID-19 vaccine, single dose use of COMIRNATY including Comirnaty (2023-2024 Formula) was supported by Study C4591044 (safety and immunogenicity) and Study C4591001 (safety); please see Section 6.1 and Section 6.3 for clinical review of the respective studies. For individuals not previously vaccinated with a COVID-19 vaccine, the effectiveness of a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) in vaccinated individuals 12-17 years of age was extrapolated from Study BNT162-17

(immunogenicity) data in vaccinated individuals ≥18 years of age; please see Section 6.4 for clinical review of this study.

9.1.4 Immunocompromised Patients Including Patients with Human Immunodeficiency Virus (HIV) Infection

Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination and individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention were excluded from participation in Studies C4591044, C4591031, C4591001, and BNT162-17. Examples of conditions resulting in exclusion included but were not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjogren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

Based on published reports of low antibody responses and breakthrough infections among significantly immunocompromised individuals (mainly solid organ transplant recipients) who received the 2-dose primary series under EUA, FDA amended the EUA for the Pfizer COVID-19 Vaccine in August 2021 to allow for additional vaccine doses.

Safety and immunogenicity data are available for 250 individuals with HIV infection (total of 200 participants in Study C4591001 and 50 participants in Study C4591031) on stable antiretroviral therapy; all the participants had stable viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment. Study C4591031, Substudy A enrolled a total of 50 participants with HIV infection (BNT162b2 (Original) group, n=26; placebo group, n=24), and the safety data was summarized separately. The frequency of any AE after booster vaccination was 3.8% in the BNT162b2 (Original) group (n=1) and 4.2% in the placebo group (n=1) among HIV-positive participants. These numbers are too small to make definitive conclusions. Study C4591001 enrolled a small subgroup (N=200) of participants with HIV infection on stable antiretroviral therapy; these participants all had stable viral load <50 copies/mL and CD4 count >200 cells/mm^3 within 6 months before enrollment, and their data were reviewed in a previous memo.

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to COMIRNATY.

Please refer to Section 8.6 of U.S. Package Insert.

9.1.5 Geriatric Use

The safety and effectiveness of Comirnaty (Original monovalent), BNT162b2 (Original), and BNT162b2 Bivalent vaccines are relevant to COMIRNATY including Comirnaty (2023-2024 Formula) because these vaccines are manufactured using a similar process.

Of the total number of BNT162b2 (Original) in Study C4591001 as of March 13, 2021, of the 22,026 participants, 20.7% (n=4,552) were 65 years of age and older and 4.2% (n=925) were 75 years of age and older. In Study C4591031, of 5081 recipients who received BNT162b2 (Original) Dose 3, 23.1% (n=1175) were ≥65 years of age and 5.2% (n=265) were ≥75 years of age. In Study C4591044, of 726 recipients who received BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) Dose 4, 21.9% (n=159) were ≥65 years of age and 4.8% (n=35) were ≥75

years of age. No overall differences in safety or effectiveness were observed between these recipients and younger recipients.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of COMIRNATY including Comirnaty (2023-2024 Formula), 30 µg, administered as a single dose to individuals ≥12 years of age regardless of prior COVID-19 vaccination status, for prevention of COVID-19 caused by SARS-CoV-2. The safety and effectiveness data accrued with BNT162b2 (Original) and BNT162b2, Bivalent (Original and Omicron BA.4/BA.5) are pertinent because these vaccines are manufactured using a similar process as COMIRNATY including Comirnaty (2023-2024 Formula). Four studies were submitted in support of this sBLA, and taken together the studies evaluate the safety, tolerability and efficacy of a single dose of COMIRNATY, including Comirnaty (2023-2024 Formula), in individuals ≥12 years of age regardless of previous vaccine history.

Study C4591044 was an interventional, randomized, active-controlled, Phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA-based vaccine candidates as Dose 4 in COVID-19 vaccine-experienced healthy individuals (≥12 years of age). The interim CSR contained 1-month safety and immunogenicity data of participants ≥12 years of age. The primary and secondary objectives were met in all participants with and without evidence of prior SARS-CoV-2 infection. The safety profile was comparable to the safety profile of BNT162b2 (Original).

Study C4591031 was a Phase 3 study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2 (Original). The review focused on the safety evaluation of Substudies A and C only. Substudy A reported 6-month data from participants who received Dose 3 of BNT162b2 (Original), 30 µg after completing two previous doses of the study vaccine and enrolled participants ≥16 years of age (BNT162b2 (Original) group, n=5081; placebo group, n=5044). Substudy C reported 1-month data from participants who received Dose 3 of BNT162b2 (Original), 30 µg after completing two previous doses of the study vaccine and enrolled participants 12-17 years of age.

Overall, for Substudy A, the AE profile after Dose 3 reflected mostly reactogenicity events and did not suggest any new clinically important short-term safety concerns for Dose 3 of BNT162b2 (Original), 30 µg. Most AEs were mild or moderate in severity. Few SAEs were reported overall and showed no imbalance between the BNT162b2 (Original), 30 µg and placebo groups (0.8% and 0.7%, respectively, during the blinded placebo-controlled follow-up period). The tolerability and safety profile of BNT162b2 (Original), 30 µg in participants ≥16 years of age at up to 6 months after Dose 3 (to the data cutoff date) was acceptable and consistent with results previously reported. Substudy C reactogenicity profile of Dose 3 of BNT162b2 (Original), 30 µg among adolescents 12-17 years of age reflected short-lived reactions with typical onset 1 to 2 days after Dose 3 and resolution within 1 to 2 days of onset. The most frequently reported local reaction was IS pain; the most frequently reported systemic events were fatigue, headache, and muscle pain. The overall pattern of reactogenicity after a BNT162b2 (Original), 30 µg booster was comparable to that observed after the previous two doses of BNT162b2 (Original), 30 µg. No related SAEs, death, or AEs leading to withdrawal were reported up to 1-month post-Dose 3. The tolerability and safety profile of BNT162b2 (Original), 30 µg in participants 12-17 years of age was generally acceptable.

Study C4591001 was a Phase 1/2/3 study of SARS-CoV-2 RNA vaccine candidates, initiated in April 2020. Phase 2/3 evaluated efficacy of BNT162b2 (Original), 30 µg, and provided additional safety, efficacy, and immunogenicity data which were the evidentiary basis for initial licensure. The study was amended to evaluate the "boostability" (Dose 3) of BNT162b2 (Original). The 12-15 years of age group data were reported on 825 participants who received BNT162b2 (Original), 30 µg Dose 3 after completing two previous doses of the study vaccine. In the 18-55 years of age group 6-month data were reported on 306 participants who received BNT162b2 (Original), 30 µg Dose 3 after completing 2-dose "primary" series of the study vaccine. The data from the participants 12-15 years of age who received BNT162b2 (Original), 30 µg Dose 3 showed that administration of the third dose was generally safe and well-tolerated, based on the AE profile up to 9.5 months median follow-up after Dose 3. The AE profile among adolescents reflected expected reactogenicity events, age-appropriate events consistent with the general population, with low incidence of severe events. The incidence of SAEs in adolescents was low. No deaths occurred in the adolescent group. Review of AEs and SAEs suggested no new patterns or new safety signals among adolescents, which continues to support the safety of BNT162b2 (Original) administered as Dose 3 to individuals 12-15 years of age. The data from the participants 18-55 years of age who received BNT162b2 (Original), 30 µg Dose 3 showed that local and systemic reactogenicity events were common, well-tolerated, and short-lived (median durations of 1.0 to 2.0 days). Most reactogenicity events were mild or moderate in severity. Participants with SAEs within 6 months after vaccination were low (≤0.7%), and all SAEs were assessed by the investigator and FDA as not related to study intervention. There were no AEs leading to withdrawal or deaths reported. BNT162b2 (Original), 30 µg, Dose 3 administered to individuals who received 2 previous doses, was shown to be safe and tolerable, consistent with reactogenicity and safety profile observed for BNT162b2 (Original) 30 µg. Long-term safety data ≥6 months post-BNT162b2 (Original), 30 µg Dose 3 did not reveal any new safety concerns.

Study BNT162-17 post-hoc analysis evaluated the immunogenicity of a SARS-CoV-2 bivalent RNA-based vaccine in healthy participants to address the single dose use in vaccine-naïve seropositive individuals. Immunobridging analysis of the efficacy demonstrated in the original Study C4591001 was done by comparison of the reference strain immune response in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection at 3 weeks after a single dose of BNT162b2 Bivalent (B.1.1.7 + B.1.617.2, encoding Alpha and Delta S proteins, respectively) with immune response at 1 month after 2 doses of the BNT162b2 (Original) vaccine in participants without evidence of prior infection. This analysis demonstrated that in individuals 18-85 years of age, a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2) in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection could be expected to have at least noninferior efficacy to 2 doses of the BNT162b2 (Original) vaccine in participants without evidence of prior infection based upon: 1) noninferiority of the reference strain immune response based on GMR and 2) a finding of the lower bound of the 2-sided 95% CI of the percent difference in SRR of -10.04% to support noninferiority in the setting where a prespecified NI was 10.0%. The totality of this immunogenicity data supports the conclusion that a single dose of COMIRNATY including Comirnaty (2023-2024 Formula) is potentially as effective for seropositive COVID-19 vaccine-naïve individuals as two doses in seronegative COVID-19 vaccine-naïve individuals. These data and the common dose for the 12-17 years of age group supported extrapolation of vaccine effectiveness of COMIRNATY including Comirnaty (2023-2024 Formula) to individuals 12 through 17 years of age.

The clinical data submitted meet FDA's statutory evidence of effectiveness standards and safety standards to support licensure of COMIRNATY including Comirnaty (2023-2024 Formula) for the prevention of COVID-19, including relevant efficacy success criteria and numbers of

vaccinated study participants and follow-up time for an acceptable safety database. The clinical data submitted in this application, together with the quantitative benefit-risk assessment summarized in this review, support approval of COMIRNATY including Comirnaty (2023-2024 Formula), 30 µg for the indication of active immunization to prevent symptomatic COVID 19 caused by SARS-CoV-2 in individuals 12 years of age and older. In the clinical trials, local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the BNT162b2 (Original) group than the placebo group. Overall, deaths and SAEs were reported by similar proportions of participants in both groups. Adverse reactions other than solicited reactogenicity events identified from the clinical trial data included lymphadenopathy. The imbalance supports the continued labeling of lymphadenopathy as a potential adverse reaction.

Comirnaty (2023-2024 Formula) contains 30 µg mRNA encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5, which is better matched to currently circulating SARS-CoV-2 lineages in the U.S. than the lineages in the current FDA-authorized bivalent COVID-19 vaccines (CDC, 2023a). Therefore Comirnaty (2023-2024 Formula) is anticipated to be clinically effective against the predominant circulating strain.

Based on the totality of data and the benefit-risk considerations as described in Section 11 below, the clinical reviewers conclude that the clinical trial data submitted in this application, and complemented by plans for post-licensure studies, support approval of COMIRNATY including Comirnaty (2023-2024 Formula), for the indication of active immunization to prevent symptomatic COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 30. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for nearly 104 million cases and 1.1 million deaths in the U.S. • There has been a succession of variants (Delta, Omicron BA.1, BA.5. and more recently XBB.1.5, among others) that have led to a reduction in vaccine effectiveness. • Although the available bivalent COVID-19 vaccines continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased.	• COVID-19 is a serious disease associated with significant acute morbidity and mortality, and in a subset of individuals, the additional morbidity from post-acute sequelae of COVID-19 (long COVID). • The emergence of variants of the SARS CoV-2 virus may lead to more transmissible viruses or more severe disease. • mRNA-based COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity.
Unmet Medical Need	• Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is one of two mRNA based COVID-19 vaccines for which an Emergency Use Authorization (EUA) has been issued. Currently, no vaccines are FDA licensed for single dose use for the prevention of COVID-19, and this has been cited as a reason for vaccine hesitancy and for some individuals declining to receive EUA vaccines. • Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity.	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19.
Clinical Benefit	• In study C4591044 (BNT162b2 (Original)-vaccine- -experienced individuals): SARS-CoV-2 responses against the B.1.1.529 (Omicron BA.4/BA.5) and USA_WA1/2020 reference strains following a single 30ug BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) Dose 3 was evaluated in the following age groups: ○ >55 years of age, compared to age-matched participants from study 1031 substudy E who received 30ug BNT162b2 (Original) ○ 18-55 years of age, compared to Study 1044 participants >55 years of age ○ 12-17 years of age: descriptive analysis Primary and secondary endpoints (GMR, seroresponse) were met (see section 6.1.13). • In study BNT162-17 (COVID-19 vaccine-naïve SARS-CoV-2 seropositive, ≥18 years of age), the noninferiority criterion following a single dose of BNT162b2 bivalent (B.1.1.7 + B.1.617.2), compared with the BNT162b2 (Original) study 1001 efficacy population after post-Dose 2, was met based on GMR, but not percentage difference in seroresponse rates (LL of 95% CI was -10.04% which is below the prespecified criteria of -10%). The higher post-study dose nAb GMTs among participants who were SARS-CoV-2 positive at baseline are expected due to prior SARS-CoV-2 exposure (i.e., hybrid immunity). Immune responses in 12-17 years of age were extrapolated from immune responses in study BNT162-17 participants ≥18 years of age.	The evidence for clinical benefit of a single dose (30 µg) of COMIRNATY including Comirnaty (2023-2024 Formula) meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 12 years of age and older.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most commonly reported adverse reactions were solicited local and systemic reactions (injection site pain, fatigue, headache, chills, muscle pain, fever, and joint pain) and lymphadenopathy.	• The most common risks are mild to moderate, self-limited injection site and systemic adverse reactions. • Less common but potentially serious risks include severe allergic reactions and myocarditis/pericarditis.
Risk Management	• Labeling for COMIRNATY describes the common and uncommon (but potentially serious) risks associated with the vaccine. The labeling includes warning statements for severe allergic reactions and myocarditis/pericarditis.	• Risk mitigation strategies for COMIRNATY including Comirnaty (2023-2024 Formula) use in individuals 12 years of age and older include communication of risks and benefits through labeling, directed counseling prior to vaccination according to individual risks and benefits, and a pharmacovigilance plan to further evaluate risks. • A PMC study will be conducted to evaluate immune responses following a single dose of Comirnaty (2023-2024 Formula) in individuals ≥12 years of age who have not been previously vaccinated with a COVID-19 vaccine.

11.2 Risk-Benefit Summary and Assessment

COVID-19 caused by SARS-CoV-2 is associated with a wide spectrum of manifestations, including mild illness in some individuals and severe morbidity (in some cases with long-term sequelae) and/or mortality in others. Over 6.95 million deaths attributable to COVID-19 have been reported worldwide since the beginning of the pandemic in late 2019, with >1.1 million U.S. deaths since the beginning of the pandemic and >6.2 million U.S. hospitalizations during the year up to August 2023. Since the start of the pandemic, there has been a succession of SARS-CoV-2 variants, including Beta, Delta, Omicron BA.1, and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and other Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. These interventions are generally most effective in diseases of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2, they are usually not effective for individuals with severe disease. Additionally, such treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID). While the World Health Organization in May 2023 declared the pandemic over, it was noted that it does not mean the disease is no longer a global threat. As new variants evolve and immunity wanes, there is a continued need for the evolution of vaccines and preventive efforts.

In addition to the currently authorized and approved treatments, FDA-approved and -authorized vaccines may provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech, and an adjuvanted, protein subunit vaccine from Novavax (in individuals 12 years of age and older only).

The original monovalent COVID-19 vaccines were based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. Vaccine effectiveness against symptomatic disease declined more rapidly than that against serious disease, as illustrated by studies conducted in the United States (Dorabawila et al., 2022; Lauring et al., 2022), Israel (Bar-On et al., 2022), Qatar (Chemaitelly et al., 2022), Portugal (Kislaya et al, 2022), and England (Andrews et al., 2022). In the setting of the viral variants that have emerged in the past, booster doses with available vaccines (based on the ancestral strain) were able to restore some degree of protection against serious and symptomatic disease.

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have been evaluated previously by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the U.S. due to the rapid evolution of the SARS-CoV-2 variants. Following emergence of the Omicron variant and its sublineages (BA.4/BA.5 and related sublineages) in November 2021, and based on data suggesting improved protection against Omicron sublineages conferred by the bivalent vaccines [Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5); Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] compared to the original monovalent [Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine (Original monovalent)] COVID-19 vaccines, FDA, on August 31, 2022, authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for booster doses in

individuals ≥12 or ≥18 years of age, respectively. In April 2023, the FDA authorized the use of the bivalent COVID-19 vaccines for all doses in individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65 years of age and older; and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of original monovalent COVID-19 Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.

Bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron including the BA.4/BA.5 sublineages compared with the original monovalent COVID-19 vaccines. However, the effectiveness of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines against Omicron sublineages, including the most recently circulating sublineages, appears to wane over time (refer to Section 3.1), suggesting that an updated strain composition of COVID-19 vaccines to match currently circulating Omicron sublineages more closely is warranted.

The safety and effectiveness data accrued with Pfizer-BioNTech COVID-19 Vaccine, Bivalent are relevant to Comirnaty (2023-2024 Formula), because COMIRNATY including Comirnaty (2023-2024 Formula) are manufactured using a similar process.

The scientific evidence available to support this sBLA application for licensure of COMIRNATY including Comirnaty (2023-2024 Formula) for use as a single dose in individuals 12 years of age and older irrespective of prior COVID-19 vaccination status include:

- Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which booster vaccination with the Comirnaty (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (see Section 6).
- Preclinical data demonstrating that Comirnaty (2023-2024 Formula) when administered to vaccine naive and vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) against XBB-related sublineages (see CMC review memorandum).
- Chemistry, Manufacturing and Control Information related to Comirnaty (2023-2024 Formula) including the manufacturing facilities (see CMC review memorandum).
- Postmarketing safety surveillance data of Comirnaty (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (see Pharmacovigilance review memorandum).
- Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies (see Section 5.1).

There were no new safety signals identified in the submitted safety data that are not already addressed in the Comirnaty (Original monovalent) U.S. prescribing information.

11.3 Discussion of Regulatory Options

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.5/BA.5) is currently available under EUA for use in individuals ≥12 years of age irrespective of vaccination history. The Applicant has requested, and data provided in this sBLA support, approval of the

COMIRNATY and Comirnaty (2023-2024 Formula) vaccine for single dose use in individuals ≥12 years of age to prevent COVID-19 caused by SARS-CoV-2. Seroprevalence data show that >90% of individuals ≥5 years of age have evidence of exposure to SARS-CoV-2 from infection and/or vaccination, and available real world data show that seropositive individuals respond adequately to a single dose of COVID-19 vaccine. Also, similar to influenza vaccines, the COVID-19 vaccine strain composition is revised based on epidemiological and effectiveness data. The totality of clinical data provide evidence to support the safety and effectiveness of Comirnaty with updates to the strain composition and/or valency.

11.4 Recommendations on Regulatory Actions

For the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, the clinical reviewer recommends approval of Comirnaty (2023-2024 Formula), administered as a single dose, and that this independent assessment of submitted clinical trial data serve as the basis to support the safety and effectiveness of future periodic strain updates to COMIRNATY.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed, comments were sent to the Applicant, and all issues were satisfactorily resolved. The clinical data in the final prescribing information were reviewed by the clinical reviewer and found to be consistent with and supported by data in the sBLA application. The labeling negotiations will be finalized on the day of approval. Please refer to the final package insert approved on September 11, 2023.

11.6 Recommendations on Postmarketing Action

Postmarketing safety monitoring of COMIRNATY will include routine pharmacovigilance with adverse event reporting under 21 CFR 600.80. The initial approval of Comirnaty (Original monovalent) (125752/0 approval letter dated August 23, 2021) includes postmarketing requirement studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis following administration of COMIRNATY.

The current pharmacovigilance plan, version 3.0, dated July 31, 2023, is adequate to monitor postmarketing safety for COMIRNATY including COMIRNATY (2023-2024 Formula) in accordance with 21 CFR 600.800.

As summarized in section 9.1.3, the Applicant is required to conduct following licensure the PREA deferred study listed below:
Deferred pediatric studies:
Study C4591048 Substudy E to evaluate the safety and effectiveness of a single dose of Comirnaty in children 2-11 years of age.

- Final Protocol Submission: September 1, 2023
- Study Completion: December 31, 2024
- Final Report Submission: April 30, 2025

Study C4591048 Substudy A to evaluate the safety and effectiveness of a single dose of Comirnaty in children 6 months-4 years of age.

- Final Protocol Submission: September 1, 2023
- Study Completion: May 31, 2026
- Final Report Submission: September 30, 2026

The Applicant committed to conduct the following study as a Postmarketing Commitment (PMC):
Study C4591054, Substudy B to evaluate immune responses following a single dose of Comirnaty (2023-2024 Formula) in individuals ≥12 years of age who are not previously vaccinated with a COVID-19 vaccine.

Final Protocol Submission: July 21, 2023
Study Completion: June 30, 2024
Final Report Submission: Dec 31, 2024

12 APPENDIX A. ADVERSE EVENTS OF SPECIAL INTEREST

The Applicant identified myocarditis and pericarditis, defined by the Brighton Collaboration, as the AESIs for their protocols reviewed in this sBLA. The definitions are available at the following website and were last accessed on September 10, 2023:
https://brightoncollaboration.us/myocarditis-case-definition-update/.

13 APPENDIX B: COVID-19 CASE DEFINITIONS

The Applicant's case definition used in the evaluation of vaccine efficacy for the approval of Comirnaty (Original monovalent):

Efficacy Evaluation
The case definition for a confirmed case of COVID-19 for the primary efficacy endpoint for study C4591001, was the presence of at least one of the following symptoms and a positive SARS-CoV-2 nucleic-acid amplification-based test within 4 days of the symptomatic period:

- 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

The case definition for severe COVID-19 case included a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death