BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application (sBLA)
STN	125742/656
CBER Received Date	March 18, 2025
PDUFA Goal Date	January 16, 2026
Division / Office	(b) (6) /OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	(b) (6) (b) (6) /OVRR/CBER
Review Completion Date / Stamped Date	August 27, 2025
Supervisory Concurrence	(b) (6) (b) (6) /OVRR/CBER (b) (6) (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 10 ug 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
Applicant Proposed 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 5 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANDA	Abbreviated New Drug Application
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
(b) (6)	(b) (6)
DMC	Data Monitoring Committee
DP	Drug Product
DS	Drug Substance
ECMO	Extracorporeal Membrane Oxygenation
ECG/EKG	Electrocardiogram
ED	Emergency Department
EDMC	External Data Monitoring Committee
EMS	Emergency Medical Services
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
H/H	Hemoglobin/Hematocrit
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HSP	Henoch-Schönlein Purpura
ICU	Intensive Care Unit
IM	Intramuscular
IRC	Internal Review Committee
IRR	Incidence Rate Ratio
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantitation
LNP	Lipid Nanoparticles

LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem Inflammatory Syndrome in Children
mITT	Modified Intention to Treat
MMWR	Morbidity and Mortality Weekly Report
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NAAT	Nucleic Acid Amplification Test
nAb	Neutralizing Antibody
NI	Noninferiority
NT50	50% Neutralizing Titer
NTD	N-Terminal Domain
OVRR	Office of Vaccines Research and Review
PD	Protocol Deviations
PDUFA	Prescription Drug User Fee Act
PI	Package Insert/Principal Investigator
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
PT	Preferred Term
RBD	Receptor Binding Domain
RR	Respiratory Rate
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBLA	Supplemental Biologics License Application
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SpO2	Oxygen Saturation
SRR	Seroresponse Rate
STN	Submission Tracking Number
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
US/U.S.	United States
USPI	United States Prescribing Information
VE	Vaccine Efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WBC	White Blood Cells
WHO	World Health Organization

1. Executive Summary

On March 18, 2025, BioNTech Manufacturing GmbH, Inc. and Pfizer, Inc. in partnership (the Applicant) submitted a supplemental Biologics License Application (sBLA) to the United States (U.S.) Food and Drug Administration (FDA) to support licensure of Comirnaty (10 µg) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children 5 years through 11 years of age. This application supports a single-dose regimen for children in this age group, irrespective of prior COVID-19 vaccination status. Comirnaty is a nucleoside-modified mRNA (modRNA) vaccine encoding for pre-fusion stabilized SARS-CoV-2 spike (S) glycoprotein, encapsulated in lipid particles. It is currently licensed for use as a single 30-µg dose for individuals 12 years of age and older. The original formulation of Comirnaty, hereinafter referred to as Comirnaty (Original monovalent), encoded the S protein of Wuhan-HU-1 SARS-CoV-2 strain, hereinafter referred to as the Original strain.

Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Comirnaty, is currently authorized under emergency use authorization (EUA) for administration of a single-dose regimen in children 5 years through 11 years of age, a three-dose regimen in those individuals 6 months through 4 years of age who were not previously vaccinated with a COVID-19 vaccine, a two-dose regimen in individuals 6 months through 4 years of age previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, and a one-dose regimen in individuals 6 months through 4 years of age previously vaccinated with at least two doses of Pfizer-BioNTech COVID-19 Vaccines.

This sBLA contains data from three clinical studies to support the requested indication. Study C4591007, hereinafter referred to as 1007, evaluated a 2-dose series of Comirnaty (Original monovalent) in COVID-19 vaccine-naïve children 5 years through 11 years of age (two-part design: Phase 1 [open-label dose-finding] and Phase 2/3 [blinded, saline placebo comparator]) and a single dose of Comirnaty (Original monovalent)) following the 2-dose series (open-label extension study). Study C4591048 Substudy D, hereinafter referred to as 1048 SSD, was an open-label study that evaluated a single dose of Pfizer-BioNTech COVID-19 vaccine, Bivalent (Original and Omicron BA.4/BA.5), hereinafter referred to as BNT162b2 (Bivalent Original and BA.4/BA.5), in COVID-19 vaccine-experienced children 5 years through 11 years of age. Study C4591048 Substudy E, hereinafter referred to as 1048 SSE, was an open-label study that evaluated a single dose of Comirnaty (Omicron XBB.1.5), hereinafter referred to as Comirnaty (Monovalent XBB.1.5), in COVID-19 vaccine-naïve children 5 years through 11 years of age. The sBLA included an additional study of healthy participants ≥ 65 years of age who received concomitant administration of BNT162b2 (Bivalent Original and BA.4/BA.5) and Abrysvo (RSVpreF), with and without Fluzone High-Dose, Quadrivalent seasonal influenza vaccine. This study will be reviewed in a separate clinical memo because the data were initially submitted to STN 125742/634 as a standalone sBLA and subsequently added to this submission.

Effectiveness

The primary results supporting the effectiveness of Comirnaty are from

- COVID-19 vaccine-naïve children:
  - Study 1007 Phase 2/3 blinded, placebo-controlled (N=2703, Comirnaty [Original monovalent], N=1348 saline placebo)
    The primary objective was to demonstrate that neutralizing antibody (nAb) responses in children 5 years through 11 years of age receiving 2 doses of Comirnaty (Original monovalent) formulation were noninferior to responses in young adults (16 years through 24 years of age) who received 2 doses of Comirnaty (Original monovalent)

in Study C4591001, which was the primary efficacy study supporting the original BLA for Comirnaty. The secondary objective was to evaluate the efficacy of Comirnaty (Original monovalent) against confirmed COVID-19 occurring from 7 days post-Dose 2 to pre-Dose 3 during the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection. The analysis of this secondary objective required demonstration of noninferiority in the primary analysis and accrual of at least 21 cases of COVID-19.

  - Study 1048 SSE (N=285)
    The primary effectiveness objective was to demonstrate noninferior immunogenicity of a single dose of Comirnaty (Monovalent XBB.1.5) between COVID-19 vaccine-naïve children who received a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) and vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A.

- COVID-19 vaccine-experienced children:
  - Study 1007 open-label extension (N=67, Comirnaty (Original monovalent) recipients from Study 1007)
    There was no primary effectiveness objective for the Booster Phase. All objectives for this study were descriptive immunogenicity.
  - Study 1048 SSD (N=103)
    The primary effectiveness objective was to descriptively compare the immune response between children who received BNT162b2 (Bivalent Original and BA.4/BA.5) as a fourth dose after 3 doses of Comirnaty (Original monovalent) subsequently and Study 1007 children who received 3 doses of Comirnaty (Original monovalent).

Safety
The overall safety database in children 5 years through 11 years included 3532 vaccinated participants across three studies. In the clinical studies submitted to this sBLA, local and/or systemic solicited adverse reactions (ARs) following vaccination were generally mild to moderate and short-lived (i.e., 1-2 days in duration). The most common solicited local AR was injection site pain. The most common solicited systemic ARs were fatigue, headache, and new or worsened muscle pain.

No cases of myocarditis or pericarditis were reported in Studies 1007 (placebo-controlled and open-label), 1048 SSD, and 1048 SSE. There were 21 serious adverse events (SAEs) reported; none were assessed as related to the study doses by the investigators. Rates of lymphadenopathy (unsolicited AE) were similar to those reported by adolescents 12 years through 15 years of age from Study C4591001 (Study 2), which are discussed under Section 6 of the United States Prescribing Information (USPI). There were no new safety concerns identified. No new safety PMR studies are recommended.

Conclusion
Substantial evidence of effectiveness of Comirnaty in children 5 years through 11 years of age include: (1) noninferior immunogenicity of Comirnaty (Original monovalent) compared with the responses in young adults (16 years through 24 years old) in whom clinical efficacy was demonstrated in Study C4591001, (2) vaccine efficacy of 88.2% (95% confidence interval [CI]: 76.2, 94.7) in participants without evidence of prior SARS-CoV-2 infection demonstrated against confirmed COVID-19 occurring from 7 days post-Dose 2 to pre-Dose 3 during the blinded follow-up, and (3) descriptive noninferior immunogenicity of Comirnaty (Monovalent XBB.1.5) in

COVID-19 vaccine-naïve children compared with vaccine-experienced participants ≥12 years of age who received a single licensed dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A. Safety data from Studies 1007, 1048 SSD, and 1048 SSE suggest that Comirnaty in children 5 years through 11 years of age has a similar safety profile compared with Comirnaty in adolescents and young adults (previously approved, safety data described in the USPI) absent evidence of increased risk of myocarditis/pericarditis in children under 12 years of age following vaccination. Therefore, the submitted data demonstrate a favorable benefit-risk profile and support approval of Comirnaty for COVID-19 prevention in children 5 years through 11 years of age.

Pediatric Research Equity Act (PREA)
Taken together, these data support the assessment and labeling of a single dose of Comirnaty in children 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Individual study demographics are presented in Section 6 under the subsections for each study.

Effectiveness
Analyses of vaccine efficacy and immunogenicity (although limited by small numbers in certain subgroups) did not reveal clinically meaningful differences in SARS-CoV-2 neutralizing GMT or seroresponse by sex, ethnicity, race, or for obesity or medical comorbidities associated with high risk of severe COVID-19.

Safety
Analyses of solicited local and systemic ARs and unsolicited AEs and SAEs (although limited by small numbers in certain subgroups) did not suggest clinically meaningful differences in safety by sex, ethnicity, race, or for obesity or medical comorbidities associated with high risk of severe COVID-19.

1.2 Patient Experience Data

No patient experience data were submitted in this sBLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

SARS-CoV-2 is a coronavirus that emerged in late 2019 and was first 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 June 29, 2025, SARS-CoV-2 infection has resulted in over 778 million cases of COVID-19 and over 7 million deaths worldwide (WHO, 2025). 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, 2025a), may develop severe respiratory tract disease, including pneumonia and severe acute respiratory distress syndrome, that leads to multiorgan failure and death. Most individuals with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2025b), and in rare instances children may experience a serious medical condition associated with COVID-19 called Multisystem Inflammatory Syndrome in Children (MIS-C) (CDC, 2025c).

In the U.S., more than 1.2 million deaths from COVID-19 have been reported to the CDC (CDC, 2025d), with a cumulative COVID-19-associated hospitalization rate of 77.8 per 100,000 people

for the 2024-2025 season, as of June 28, 2025 (CDC, 2025d). Individuals 65 years of age and older accounted for the majority of COVID-19 associated hospitalizations and death at the end of the 2024-2025 season (317.4 per 100,000 people) (CDC, 2025d and CDC, 2025e) and individuals 5 years through 17 years of age have the lowest hospitalization rate at 5.9 per 100,000 people, (CDC, 2025d). 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.

The SARS-CoV-2 Omicron variant has evolved into distinct sublineages with additional mutations in the spike protein gene, as well as elsewhere in the genome, leading to successive waves across the globe. In June 2023, XBB sublineages dominated, both in the U.S. and globally and accounted for >95% of the circulating virus variants in the U.S (CDC, 2025f). In June 2024, an apparent increase in the prevalence of KP.2 sublineage led FDA to advise the manufacturers of the licensed and authorized COVID-19 vaccines that the preferred JN.1-lineage for COVID-19 vaccines (2024-2025 Formula) is KP.2, if feasible (Updated COVID-19 Vaccines for Use in the United States Beginning in Fall 2024 | FDA). On May 22, 2025, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States. The committee unanimously voted to recommend a monovalent JN.1-lineage vaccine composition. Based on the totality of the evidence, FDA has advised the manufacturers of the approved COVID-19 vaccines that to more closely match currently circulating SARS-CoV-2 viruses, the COVID-19 vaccines for use in the United States beginning in fall 2025 should be monovalent JN.1-lineage-based COVID-19 vaccines (2025-2026 Formula), preferentially using the LP.8.1 strain (COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025 | FDA).

Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, SARS-CoV-2 evolution is complex and remains unpredictable. 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.

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

2.2.1 FDA-approved therapies for COVID-19

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 either 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 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

Antivirals:
Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults and authorized for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years through 17 years of age and 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 18 years of age and older 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:
Pemgarda (pemivibart) is authorized for preexposure prophylaxis for individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2; and who have moderate-to-severe immune compromise due to a medical condition or due to taking immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination.

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 or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 years 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

mNexspike (2024-2025 Formula)
mNexspike (COVID-19 Vaccine, mRNA), manufactured by Moderna, is indicated for the active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals who have been previously vaccinated with any COVID-19 vaccine and are 65 years of age and older or 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. mNexspike (2024-2025 Formula) contains nucleoside-modified mRNA encoding the N-terminal domain (NTD) and receptor binding domain (RBD) of the S protein of the SARS-CoV-2 Omicron variant JN.1, encapsulated in lipid particles. For additional information on dosing and schedule, please refer to the mNexspike Package Insert (PI). Safety and effectiveness data supporting approval of mNexspike are documented in the BLA clinical review memorandum and Summary Basis of Regulatory Action.

Nuvaxovid and Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)
Nuvaxovid (COVID-19 Vaccine, Adjuvanted) manufactured by Novavax, Inc. is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adults 65 years and older, and for individuals 12 years through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Nuvaxovid (2024-2025 Formula) contains recombinant S protein of the SARS-CoV-2 Omicron variant JN.1 and Matrix-M adjuvant. Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Nuvaxovid, is authorized under EUA for administration of a single-dose regimen at least 2 months after receipt of the last previous dose of COVID-19 vaccine to individuals 12 years of age and older previously vaccinated with any COVID-19 Vaccine. In individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, Novavax COVID-19 Vaccine (2024-2025 Formula), Adjuvanted is authorized under EUA for administration as a 2-dose regimen. Individuals with certain kinds of immunocompromise 12 years of age and older may be administered additional age-appropriate doses. Safety and effectiveness data supporting approval of Nuvaxovid are documented in the BLA clinical review memorandum.

Spikevax (2024-2025 Formula)
Spikevax (COVID-19 Vaccine, mRNA), manufactured by ModernaTX Inc., is approved for use in individuals who are: 65 years of age and older, or 6 months through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. The vaccine is administered as a two-dose series for COVID-19 vaccine-naïve individuals 6 months through 23 months of age, as a single-dose for COVID-19 vaccine-experienced individuals 6 months through 23 months of age, and as a single-dose for individuals 2 years of age and older irrespective of prior COVID-19 vaccination status. The dose is 0.25 mL for individuals younger than 12 years of age and 0.5 mL for individuals 12 years of age and older. Spikevax (2024-2025 Formula) contains nucleoside-modified mRNA encoding the viral spike of the S protein of the SARS-CoV-2 Omicron variant JN.1, encapsulated in lipid particles. Moderna

COVID-19 Vaccine (2024-2025 Formula), a formulation of the vaccine manufactured using the same process as Spikevax, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 years through 11 years of age, two-dose regimen in those individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, and a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with Moderna COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age and older may be administered additional age-appropriate doses. For additional information on dosing and schedule, please refer to the Spikevax Package Insert. Safety and effectiveness data supporting approval of Spikevax are documented in the BLA clinical review memorandum.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

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. On September 11, 2023, Comirnaty (2023-2024 Formula, Monovalent XBB.1.5) was approved for use in individuals ≥12 years of age and was authorized under EUA as Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula, Monovalent XBB.1.5) for use in individuals 6 months through 11 years of age. On August 22, 2024, Comirnaty (2024-2025 Formula, Monovalent KP.2) was approved for use in individuals 12 years of age and older and Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula, Monovalent KP.2) was authorized for individuals 6 months through 11 years of age. As of July 15, 2025, Comirnaty was approved in 83 countries and Pfizer-BioNTech COVID-19 Vaccine (inclusive of all formulations) has been used in 104 countries. In the U.S., over 464 million doses of Pfizer-BioNTech COVID-19 vaccines have been administered as of July 2025.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Major sBLA-associated regulatory activities:

- May 2024: Request for Comments and Advice on the licensure pathway for administration of Comirnaty in individuals <12 years of age; multiple communications were issued to the Applicant related to the proposed pediatric sBLA submission and on the data required to support the proposed indication.
- February 2025: Pre-sBLA meeting and follow-up; multiple communications were issued to the Applicant related to the proposed pediatric sBLA submission.
- May 22, 2025: The VRBPAC met to discuss the strain composition for the 2025-2026 Formula of COVID-19 vaccines in the U.S.

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.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Applicant responsibilities were transferred from BioNTech SE to Pfizer Inc. for the conduct of clinical studies C4591007, C4591048 Substudy D, and C4591008 Substudy E, 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.

Bioresearch Monitoring (BIMO) inspections were previously conducted for Study 1007 evaluating six clinical sites under BLA 125742/45, none of which identified deficiencies. Three clinical sites were selected for inspection for the current sBLA: 2 for 1048 SSD and 1 for 1048 SSE. The inspections did not identify deficiencies that would affect the integrity of the clinical data submitted in this BLA. Please see BIMO review memorandum for additional details.

3.3 Financial Disclosures

Table 1: Financial disclosures in Studies 1007, 1048 SSD, and 1048 SSE

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 1209
Number of investigators who are sponsor employees (including both full-time and part-time employees): 1
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10
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: 8 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): 2 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 product reviewer reviewed 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 (2025-2026 Formula). Facility information provided in the sBLA was reviewed and found to be sufficient and acceptable.

4.2 Assay Validation

CBER Product and Assay reviewers evaluated the clinical serologic assays and determined they were adequate to support licensure.

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

CBER statistical reviewers confirmed the key statistical analyses for safety, immunogenicity, and efficacy and found no major statistical issues that would impact the interpretation of the data and conclusions.

4.6 Pharmacovigilance

Pfizer is conducting safety-related post-authorization/postmarketing studies for Comirnaty (Original monovalent), BNT162b2 (Bivalent Original and BA.4/BA.5) and Comirnaty (Monovalent XBB.1.5), 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 (version 5, dated June 11, 2025) to monitor safety concerns that could be associated with the Comirnaty (2025-2026 Formula). The plan includes the following safety concerns:

- Important Identified Risks: Anaphylaxis, myocarditis, and pericarditis.
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.
- Missing Information: Use in pregnancy and while breast-feeding, long-term safety, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities, and use in subjects with autoimmune or inflammatory disorders.

The Applicant will perform routine and enhanced pharmacovigilance 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. Evidence suggests that a combination of SARS-CoV-2 infection and vaccination confers significant protection, particularly against severe COVID-19 and hospital admissions. According to CDC, the seroprevalence of SARS-CoV-2 in 2023 was estimated to be 98% in people 16 years of age and older (CDC, 2023). Similarly, among adolescents 12 years through 17 years old, children 5 years 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, 2022). Based on the substantial evidence that supported the use of single dose (30 µg) of Comirnaty in individuals 12 years of age and older irrespective of their prior COVID-19 vaccination status, FDA approved a single dose of Comirnaty in individuals 12 years of age and older in September 2023. FDA additionally sought evidence from the Applicant of the safety and effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age, irrespective of COVID-19 vaccination status. These pediatric data were submitted to this sBLA and are summarized below:

Effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status is based on:

- Immunogenicity and efficacy of 2 doses (10 µg) of Comirnaty (Original monovalent) in COVID-19 vaccine-naïve children 5 years through 11 years of age (Study 1007).
- Immunogenicity of a single dose of (10 µg) of Comirnaty (Monovalent XBB.1.5) in vaccine-naïve children 5 years through 11 years of age (Study 1048 SSE).
- Immunogenicity of a single 10-µg dose of Comirnaty (Original monovalent) in vaccine-experienced children 5 years through 11 years of age (Study 1007 Booster Phase).
- Immunogenicity of a single 10-µg dose of a BNT162b2 (Bivalent Original and BA.4/BA.5) vaccine in vaccine-experienced children 5 years through 11 years of age (Study 1048 SSD).

Safety of a single dose (10 µg) of Comirnaty including Comirnaty (2025-2026 Formula) in individuals 5 years through 11 year of age is based on the above studies.

Only safety and efficacy data in children 5 years through 11 years of age, the population for intended use, are presented in this clinical memorandum. Because the sources of pre-licensure study data to support vaccine safety and effectiveness, Studies 1007, 1048 Substudy D, and 1048 Substudy E, were conducted during times where individuals had differing prevalence of previous COVID-19 exposure and differed by vaccine administered [i.e., Comirnaty (Original monovalent) vs. BNT162b2 (Bivalent Original and BA.4/BA.5) vs. Comirnaty (Monovalent XBB1.5)], FDA agreed with the Applicant's proposal not to include integrated summaries of efficacy or safety in the BLA submission. Consequently, the sections of the clinical memo usually reserved for review of these integrated summaries (Sections 7 and 8) are not applicable.

Post-authorization effectiveness data from observational studies referenced in Section 2 and Section 11 are limited to published literature and were not submitted as part of the licensure application. Therefore, FDA has not independently reviewed and confirmed the data or assessed the study designs for potential sources of bias.

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 125742/656. The following sections were reviewed in support of this application:

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

During the BLA review period, the Applicant submitted a total of 24 amendments in response to CBER's requests for clinical information.

Table 2. Amendments, Supplemental BLA 125742/656

Amendment Number	Date Received	Description of Contents
5	May 13, 2025	Response to request for revised USPI with updated annotations
7	June 10, 2025	Response to 6/6/2025 IR regarding submission of CMC and nonclinical data to support 2025-2026 Formula for the revised indication usage statement
9	June 20, 2025	Response to 6/6/2025 IR regarding PMC concept sheet
11	June 30, 2025	Response to request to revise sections 6.1 and 14 of the USPI
12	July 3, 2025	Response to request for additional safety data regarding cases in 1048 SSD and 1048 SSE
13	July 3, 2025	Response to 6/26/2025 IR regarding C4591048 SSE and SSD clinical issues
14	July 10, 2025	Response to request for additional subgroup immunogenicity data analyses in 1048 SSE and 1054 SSA
17	July 16, 2025	Response to 7/11/25 PI labeling
19	July 16, 2025	Response to 7/16/2025 IR RE PI labeling
20	July 17, 2025	Response to 7/16/2025 IR RE PI labeling
26	August 1, 2025	Response to request for additional global approval and use data for Comirnaty
30	August 8, 2025	Response to 8/1/2025 IR RE editorial revision to USPI and submission of 30mcg PFS container label
31	August 8, 2025	Response to 8/6/2025 IR RE CBER OCD PMC #2 study design
32	August 13, 2025	Response to 7/24/2025 IR RE CBER OCD PMC 1
34	August 19, 2025	Response to 8/15/2025 IR RE proposed revision to PMC #1
35	August 20, 2025	Request to W/D STN 125742/634 info (amendment 22) and revised PI
36	August 21, 2025	Response to 8/20/2025 IR RE USPI revisions

Amendment Number	Date Received	Description of Contents
37	August 22, 2025	Response to 8/21/2025 CBER OCD request for information regarding PCVS and PMC #2
38	August 22, 2025	Response to 8/21/2025 IR RE revised DHPC letter and request for distribution plan
39	August 22, 2025	Response to 8/21/2025 IR RE regarding PMC Study 1 and PMC Study 3
40	August 25, 2025	Response to 8/22/2025 IR RE w/d of amendment 29 RE Study C5481001
41	August 25, 2025	Response to 8/22/2025 IR RE revised date on DCHP Letter
43	August 26, 2025	Response to 8/26/2025 IR RE PI and DHCP Letter distribution plan
44	August 26, 2025	Response to 8/25/2025 IR RE PMC studies and milestones

Source: FDA-generated table from amendments to STN#125742/656.

The information submitted with the listed amendments satisfactorily addressed all clinical requests sent during the review period, and salient responses from the amendments were incorporated into this memorandum.

5.3 Table of Studies/Clinical Trials

Clinical studies submitted to support the safety and effectiveness of Comirnaty are summarized in Table 3 below. In these studies, children received a single dose, 2-dose series 3 weeks apart, and/or an additional single dose referred to as a "booster dose."

Table 3. Clinical Trials Submitted in Support of Effectiveness and Safety Determinations of Comirnaty in Children 5 years Through 11 Years of Age

Study Number Blinding Purpose	Children Vaccinated (N)	COVID-19 Vaccination Status	BNT162b2 Formulation Valency Strain(s)	Number of Doses (10 µg)
C4591007 Blinded, Randomized, Placebo-Controlled Safety, Immunogenicity, Efficacy	3109	Naïve	Monovalent Original (Wuhan-Hu-1)	2
C4591007 Booster Phase Open Label Safety, Immunogenicity	2408	Experienced	Monovalent Original (Wuhan-Hu-1)	1
C4591048 SSD Open Label Safety, Immunogenicity	113	Experienced	Bivalent Original (Wuhan-Hu-1), Omicron BA.4/BA.5	1
C4591048 SSE Open Label Safety, Immunogenicity	310	Naïve	Monovalent Omicron XBB.1.5	1

Sources: STN 125742/656; FDA-generated table

Abbreviations: N=total number of vaccinated children

5.4 Consultations

5.4.1 Advisory Committee Meetings

The 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. On May 22, 2025, the VRBPAC met in open session to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States. The committee unanimously voted to recommend a monovalent JN.1-lineage vaccine composition. Based on the totality of the evidence, FDA has advised the manufacturers of the approved COVID-19 vaccines that to more closely match currently circulating SARS-CoV-2 viruses, the COVID-19 vaccines for use in the United States beginning in fall 2025 should be monovalent JN.1-lineage-based COVID-19 vaccines (2025-2026 Formula), preferentially using the LP.8.1 strain (COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025 | FDA). The Applicant has selected LP.8.1 as the JN.1-lineage composition for the 2025-2026 Formula.

5.5 Literature Reviewed

Centers for Disease Control and Prevention (CDC). 2022. Nationwide Commercial Lab Pediatric Antibody Seroprevalence. Accessed July 21, 2025. https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence.

Centers for Disease Control and Prevention (CDC). 2023. 2022-2023 Nationwide COVID-19 Infection- and Vaccination-Induced Antibody Seroprevalence (Blood donations). Accessed July 21, 2025. CDC COVID Data Tracker: 2022-2023 Nationwide Blood Donor Seroprevalence https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022.

Centers for Disease Control and Prevention (CDC). 2025a. Underlying Medical Conditions Associated with Higher Risk for Severe COVID 19: Information for Healthcare Professionals. Website updated 2/6/2025. Accessed July 21, 2025. https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

Centers for Disease Control and Prevention (CDC). 2025b. Post-COVID Conditions: Overview for Healthcare Providers. Website updated 2/3/2025. Accessed July 21, 2025. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html.

Centers for Disease Control and Prevention (CDC). 2025c. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Website updated 6/4/2025. Accessed July 21, 2025. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance.

Centers for Disease Control and Prevention (CDC). 2025d. COVID Data Tracker [database on the Internet]. Atlanta, GA: U.S. Department of Health and Human Services. Accessed July 21, 2025. https://covid.cdc.gov/covid-data-tracker.

Centers for Disease Control and Prevention (CDC). 2025e. Current Epidemiology of COVID-19. Presentation for the Advisory Committee on Immunization Practices (ACIP). Accessed July 21, 2025. https://www.cdc.gov/acip/downloads/slides-2025-06-25-26/04-Meyer-COVID-508.pdf.

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Ko HY, Yoon D, Kim JH, Jeong HE, Hong SB, Shin WC, Shin JY. Risk of new-onset seizures following immunization against COVID-19: a self-controlled case-series study. *Epidemiol Health*. 2025 May 2:e2025024. doi: 10.4178/epih.e2025024. Epub ahead of print. PMID: 40340265.

Liu, Y., He, J., Zhou, X., Wu, Y., Cai, H., Sun, Y., & Cui, X. (2024). Analysis of new-onset seizures following use of COVID-19 vaccinations in children based on VAERS. *Expert Opinion on Drug Safety*, 24(2), 177–182. https://www.tandfonline.com/doi/10.1080/14740338.2024.2348568?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

World Health Organization. (2025) Coronavirus (COVID-19) Dashboard. COVID-19 cases | WHO COVID-19 dashboard. Accessed July 20, 2025.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study C4591007 (Study 1007)

NCT04816643
"A Phase 1, open-label dose-finding study to evaluate safety, tolerability, and immunogenicity and Phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children"

Study Overview
Study 1007 evaluated safety, immunogenicity and efficacy of multiple dose levels and dose regimens in individuals 6 months through 15 years of age. The study was initiated March 24, 2021, and the last patient last visit was December 8, 2023. Data from this study were submitted across six interim and one final clinical study report (CSR) dating from September 30, 2021, through April 17, 2024.

> *Reviewer Comment: Data for individuals 12 years of age and older have been reviewed in other sBLAs previously and Comirnaty is licensed for single-dose use in individuals 12 years of age and older. Although Study 1007 evaluated individuals 6 months through 15 years of age, this clinical review will focus on safety, immunogenicity, and efficacy results obtained among children 5 years through 11 years of age because this age range corresponds to the expanded indication requested by the Applicant in this sBLA.*

6.1.1 Objectives (Primary, Secondary)

Phase 1
Primary: To describe the safety and tolerability profile of prophylactic Comirnaty (Original monovalent) at each dose level in each age group.

Endpoints: Solicited local adverse reactions for up to 7 days following each dose (injection site pain, redness, swelling), solicited systemic adverse events (AE) for up to 7 days following each dose (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), AEs for up to 1 month after each dose, serious adverse events (SAEs) for up to 6 months after last dose

Secondary: To describe the immune responses elicited by prophylactic Comirnaty (Original monovalent) at each dose level in each age group.

Endpoints: Geometric mean SARS-CoV-2 neutralizing titers (GMT) at each time point

Phase 2/3

Primary Safety: To define the safety profile of prophylactic Comirnaty (Original monovalent) in all children (selected-dose and obtaining-serum-samples-for potential-troponin I-testing portions of the study) in each age group.

Endpoints: Solicited local adverse reactions for up to 7 days following each dose (injection site pain, redness, swelling), solicited systemic AE for up to 7 days following each dose (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), AEs for up to 1 month after each dose, SAEs for up to 6 months after last dose

Primary Immunogenicity (2-dose series): To demonstrate noninferiority of the immune responses elicited by prophylactic Comirnaty (Original monovalent) between Phase 2/3 children at the dose selected for each age group and young adults 16 years through 24 years of age from the C4591001 study (in which Comirnaty (Original monovalent)) efficacy was demonstrated) without serological or virological evidence of past SARS-CoV-2 infection:

- Children 5 years through 11 years of age compared with young adults 16 years through 24 years of age from Phase 2/3 of the C4591001 study.
  Endpoints:
  - Geometric mean ratio (GMR): the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in participants from each age group (6 months through 23 months, 2 years through 4 years, and 5 years through 11 years of age) to those in young adults 16 years through 24 years of age 1-month post-Dose 2 from Phase 2/3 of the C4591001 study.
  - Seroresponse: the difference in percentages of seroresponse (defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the lower limit of quantitation [LLOQ], the post-vaccination measure of ≥4 × LLOQ is considered seroresponse) between each age group (6 months through 23 months, 2 years through 4 years, and 5 years through 11 years of age) and young adults 16 years through 24 years of age from Phase 2/3 of the C4591001 study.

Secondary Immunogenicity: To describe the immune responses elicited by prophylactic Comirnaty (Original monovalent) at the dose level selected for each age group in Phase 2/3 participants without serological or virological evidence of past SARS-CoV-2 infection.

Endpoints: SARS-CoV-2 neutralizing GMT in participants from each age group at baseline, 1-month post-Dose 2, on the day of Dose 3, and 1-month post-Dose 3. Geometric Mean Fold Rise (GMFR) in participants from each age group pre-Dose 1 to each subsequent time point post-Dose 2 or Dose 3

Secondary Efficacy (2-Dose Series): (a) To evaluate the efficacy of prophylactic Comirnaty (Original monovalent) against confirmed COVID-19 occurring from 7 days post-Dose 2 to pre-Dose 3 during the blinded follow-up period in children 5 years through 11 years of age without evidence of past SARS-CoV-2 infection, if immunobridging is successful and if at least 21 cases are accrued.

Endpoints: Confirmed COVID-19 incidence from 7 days post-Dose 2 to pre-Dose 3 per 1000 person-years of blinded follow-up

(b) To evaluate the efficacy of prophylactic Comirnaty (Original monovalent) against confirmed COVID-19 occurring from 7 days post-Dose 2 to pre-Dose 3 during the blinded follow-up period in children 5 years through 11 years of age with or without evidence of past SARS-CoV-2 infection, if immunobridging is successful and if at least 21 cases are accrued.

6.1.2 Design Overview

Study 1007 was a Phase 1/2/3 study in healthy children and young adults.

Phase 1 was the open-label dose-finding portion of the study that evaluated safety, tolerability, and immunogenicity of Comirnaty (Original monovalent) administered on a 2-dose schedule in up to 3 age groups (5 years through 11 years of age, 2 years through 4 years, and 6 months through 23 months). Dependent upon safety and/or immunogenicity data generated during this study, it was possible that dose levels would not be evaluated, would be terminated early, and/or dose levels below the lowest specified dose would be added (Table 4). As part of protocol amendment 6, all participants received a third dose of Comirnaty (Original monovalent).

Table 4: Study 1007 Phase 1 Enrollment

Age Group	6 months through 23 months	2 years through 4 years	5 years through 11 years	Total
Dose Level	3 µg	3/10 µg	10/20/30 µg	--
Participants	16[a]	16/32[a]	16/16/16 [b]	112

Source: adapted from STN125742/656, c4591007-protocol.pdf Table 1
a. Actual number of participants recruited in the ≥6 months to <2 years and ≥2 to <5 years age groups.
b. Actual number of participants recruited in the ≥5 to <12 years age group. Dose 1: 16 out of 16 received 30-µg dose level; Dose 2: 4 out of 16 received 30-µg dose level and 12 of 16 received 10-µg dose level.

> *Reviewer Comment: Selection of the dose level for further evaluation (10 µg) was based on safety and immunogenicity data from Phase 1 of the study based on increased incidence of reactogenicity observed with increasing dose level and comparable immunogenicity observed at both (10 and 20 µg) dose levels.*

Phase 2/3 evaluated safety, tolerability, and immunogenicity of the dose levels selected for each age group from Phase 1. Efficacy was evaluated within age groups with successful immunobridging, depending on accrual of sufficient cases in those age groups. Immunobridging to young adults 16 years through 24 years of age in Study C4591001 (placebo-controlled study in which Comirnaty (Original monovalent) efficacy was demonstrated) was based on immunogenicity data collected at (1) baseline and 1-month post-Dose 2 and (2) baseline and 1-month post-Dose 3. Persistence of vaccine-specific immune response in study participants was evaluated for the following intervals: (1) baseline and 1- and 6-month post-Dose 2 and (2) baseline and 1, 6, 12, and 18 months post-Dose 3. Efficacy against confirmed COVID-19 infection was also assessed.

Unblinding occurred at the 6-month follow-up visit post-Dose 2. Placebo recipients were offered the opportunity to receive Comirnaty (Original monovalent) as part of the open-label extension of Study 1007. If participants in any country became eligible for receipt of Comirnaty (Original monovalent) or another COVID-19 vaccine according to local or national recommendations prior to the 6-month follow-up visit, then all placebo recipients in the study, regardless of their country of residence, had the opportunity to receive Comirnaty (Original monovalent) at age-appropriate doses (10 µg or 3 µg) based on age at the time of the vaccination.

The initial enrollment plan for the 5 years through 11 years of age group was 2250 randomized in a 2:1 ratio to receive active vaccine or placebo. In Protocol Amendment 2 (August 6, 2021), the sample size was doubled for this age group bringing the target to 4500 individuals randomized 2:1. Unblinding was completed prior to the 6-month post-Dose 2 study visit after the FDA issued an EUA (October 29, 2021) in the US and after the implementation of protocol amendment 3 outside of the US. In protocol amendment 6, all participants received a third dose of Comirnaty (Original monovalent). For all participants (5 years through 11 years and 12 years through 15 years of age), the third dose would occur at least 6 months post-Dose 2 (updated to at least 5 months for US participants as part of protocol amendment 8). The dose level of the second and third doses of Comirnaty (Original monovalent) was based on age at the time of vaccination: children 5 years through 11 years of age at the time of the second/third dose received the 10-µg dose level, and participants ≥12 years of age at the time of the second/third dose received the 30-µg dose level.

6.1.3 Population

Key Inclusion Criteria: Healthy males and females 6 months through 11 years of age, participants' parent(s)/legal guardian(s) and participants willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures, negative urine pregnancy test for female participants biologically capable of having children, female participant of childbearing potential or male participant able to father children willing to use a highly effective method of contraception, and the participant or participant's parent(s)/legal guardian is capable of giving signed informed consent.

Key Exclusion Criteria: Phase 1 only: Past clinical (based on COVID-19 symptoms/signs alone if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19; Known infection with HIV, HCV, or HBV; Phases 1/2/3: receipt of medications intended to prevent COVID-19; previous or current diagnosis of MIS-C; other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation; history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s); immunocompromised individuals with known or suspected immunodeficiency; individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention; bleeding diathesis or condition associated with prolonged bleeding; female who is pregnant or breastfeeding; previous vaccination with any coronavirus vaccine; individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids; receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies, from 60 days before study intervention administration, or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study

6.1.4 Study Treatments or Agents Mandated by the Protocol

Intervention name: Comirnaty (Original monovalent) (BNT162 RNA-LNP vaccine utilizing modRNA)
Unit dose strength: 250 µg/ 0.5 mL
Dosage Level: 10 µg
Route of Administration: IM injection
Dosing Regimen: 2 doses (1 at baseline and then 1, at least 21 days later); a third dose was added at least 6 months post-Dose 2 in protocol amendment 6.
Placebo: Normal saline (0.9% sodium chloride)

6.1.5 Directions for Use

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

6.1.6 Sites and Centers

Study 1007 enrolled all age groups (6 months through 11 years) at a total of 119 sites in the US, Spain, Finland, Poland, Mexico, and Brazil. Mexico and Brazil did not enroll children 5 years through 11 years of age.

6.1.7 Surveillance/Monitoring

Study 1007 used an internal review committee (IRC) to review data to facilitate dose selection in Phase 1. An independent external Data Monitoring Committee (DMC) reviewed unblinded safety data routinely and on an *ad hoc* basis.

The following primary safety endpoints were collected for participants in Phase 1 and Phase 2/3:

- Local reactions (redness, swelling, and pain at the injection site) for up to 7 days following each dose
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) for up to 7 days following each dose
- AEs from Dose 1 through 1-month post-Dose 2
- SAEs from Dose 1 through 6 months post-Dose 2
- AEs from Dose 3 through 1-month post-Dose 3
- SAEs from Dose 3 through 6 months post-Dose 3
- Adverse Events of Special Interest (AESI) assessed through 6 months post-Dose 3; 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.

The safety parameters also included reactogenicity e-diary reports of local reactions and systemic events (including fever) and use of antipyretic medication within 7 days after administration of the study intervention.

6.1.8 Endpoints and Criteria for Study Success

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: The sample sizes for Phase 1 and Phase 2/3 portions of Study 1007 were not based on statistical hypothesis testing. The Phase 2/3-selected dose portion of the study was planned to randomize approximately 4500 participants (randomization ratio of 2:1 so that 3000 received active vaccine and 1500 received placebo) for each age group, with a total of approximately 13,500 participants.

Immunogenicity Analyses: The population for the primary immunobridging assessment of the 2-dose series was comprised of participants with 1-month post-Dose 2 blood sample collection in

the Phase 2/3 portion of Study 1007 and a random subset of approximately 300 Comirnaty (Original monovalent) recipients 16 years through 24 years of age from Study C4591001. A sample size of 225 evaluable participants per age group was estimated to provide a power of 90.4% to declare immunobridging success in terms of nAb GMR at 1-month post-Dose 2 for children compared with young adults. Assuming a 25% non-evaluable rate, the target enrollment was estimated as 450 participants (300 in the active vaccine group and 150 in the placebo group) for each age group with 1-month post-Dose 2 blood sample collection to achieve 225 evaluable recipients of vaccine at the selected dose. Assuming a true response rate of 90% in each comparator group, a sample size of 225 evaluable participants per group at each dose was estimated to achieve 92.6% power to show the immunobridging based on seroresponse rate using a 10% margin.

Efficacy Objectives: For vaccine efficacy (VE) evaluation after the 2-dose series for the 5 years through 11 year age group, with a total of approximately 4500 children 5 years through 11 years of age (3000 children randomized to the vaccine group and 1500 children randomized to the placebo group), assuming 25% of the participants being non-evaluable and 1.3% annual attack rate, approximately 11 first confirmed COVID-19 illness cases would be observed within 6 months after vaccination. This provides approximately 35.1% power to conclude true VE >30% with assumptions of a true VE of 80%. Since at least 21 cases would be needed to achieve 77.0% power, hypothesis testing would be conducted only if at least 21 cases accrued in the age group in which immunobridging is shown to be successful. VE against confirmed COVID-19 was estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years of blinded follow-up in the Comirnaty (Original monovalent) group to the corresponding illness rate in the placebo group. VE is reported with a 2-sided 95% CI derived using the Clopper-Pearson method adjusted for surveillance time.

Safety Analyses: Safety analyses were descriptive. The percentages of participants reporting each AE were summarized by study group. AEs and SAEs were categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms.

6.1.10 Study Population and Disposition

Study 1007 was initiated March 24, 2021, and the last patient last visit was December 8, 2023.

Phase 1: A total of 48 (98.0%) participants assigned to the 10-µg, 20-µg, and 30-µg dose level groups (N=16 each) received 2 doses of Comirnaty (Original monovalent) and completed the Month 1 post-Dose 2 visit. One participant assigned to the 20-µg dose level group did not receive Comirnaty (Original monovalent). No participants were withdrawn from the 2-dose group in Phase 1. Due to the reactogenicity observed in the first 4 of 16 participants for the assigned 30-µg dose level group after receiving both doses, the IRC decided to discontinue the 30-µg dose level and have the remaining 12 of 16 participants in the dose-level group receive 10 µg (dose selected for Phase 2/3) for Dose 2. In the 4 of 16 who received both 30-µg doses of Comirnaty (Original monovalent), pain at the injection site was reported by all 4 after both doses. Redness was reported in all 4 post-Dose 1 and 3 of 4 post-Dose 2 (1 severe). Swelling was reported by 2 of 4 participants after each dose (mild to moderate). Fever up to 38.9 °C after the second dose of vaccine developed in 4 of 4 participants. These 4 participants also reported mild to moderate fatigue and muscle pain post-Dose 1; post-Dose 2 fatigue was reported in all 4 participants while muscle pain became moderate in severity in 2 of 4 participants. Headache was mild to moderate in 3 of 4 participants post-Dose 1 and Dose 2. Vomiting and diarrhea were absent post-Dose 1 but were reported in 1 and 2 participants, respectively, post-Dose 2.

The high frequency of local and systemic reactions for these first 4 sentinel participants at Dose 2 contributed to the IRC decision to discontinue the 30-µg dose level.

Overall, 40 (81.6%) received Dose 3. All participants in the 10-µg and 30-µg groups received Dose 3, and 8 (47.1%) of participants in the 20-µg group received Dose 3 of Comirnaty (Original monovalent). A total of 40 participants (81.6%) withdrew from the study for reasons unrelated to safety (i.e., protocol deviations (42.9%) and other (30.6%)). All 15 participants who withdrew for "other" reasons, withdrew to be enrolled in Study C4591048.

Phase 2/3: Participants were randomized 2:1 to receive 10 µg of Comirnaty (Original monovalent) (n=3108) or placebo (n=1539); 99.7% received Dose 1 and Dose 2. Two (2) Comirnaty (Original monovalent) recipients (0.1%) and 2 placebo recipients (0.1%) discontinued from the vaccination period but continued in the study for safety follow-up. Most participants across both groups completed the visit at 1-month post-Dose 2 (98.5%). Among participants who discontinued from the vaccination but continued in the study, only 1 of the discontinuations was reported as due to an AE. Fourteen Comirnaty (Original monovalent) recipients (0.5%) and 12 placebo recipients (0.8%) withdrew from the study post-Dose 1. None of these withdrawals were reported as due to an AE; most (18/26) were withdrawn by parent or guardian. The median follow-up time during the original blinded follow up period from Dose 2 to Dose 3 or cutoff date was 1.9 months (range 0.1, 7.5).

Approximately half of the Comirnaty (Original monovalent) recipients (51.3%) and placebo recipients (41.0%) received Dose 3 and completed the study. A total of 1504 (48.1%) Comirnaty (Original monovalent) recipients and 903 (58.1%) placebo recipients withdrew from the study for non-safety reasons in both Comirnaty (Original monovalent) and placebo groups (i.e. due to withdrawal by parent/guardian/participant (26.1% and 35.0%, respectively) and protocol deviation (15.2% and 17.5%, respectively)). The overall median time interval to Dose 3 administration post-Dose 2 was 7.9 months.

6.1.10.1 Populations Enrolled/Analyzed

Analysis sets included:

- Enrolled: All participants who have a signed parent/guardian consent/assent
- Randomized: All participants who are assigned a randomization number in the randomization system.
- Evaluable immunogenicity (2-dose): All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
- Evaluable immunogenicity (3-dose): All eligible randomized participants who receive 3 doses of the vaccine to which they are randomized with Dose 2 and Dose 3 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
- All-available immunogenicity: All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
- Evaluable efficacy (2-dose): All eligible randomized participants who receive 2 doses of the vaccine to which they are randomized within the predefined window and have no other important protocol deviations as determined by the clinician.

- Evaluable efficacy (3-dose): All eligible randomized participants who receive 3 doses of the vaccine to which they are randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
- All-available efficacy (modified intention to treat; mITT):
    - Dose 1 all-available efficacy: All randomized participants who receive at least 1 vaccination.
    - Dose 2 all-available efficacy: All randomized participants who complete 2 vaccination doses.
    - Dose 3 all-available efficacy: All randomized participants who complete 3 vaccination doses.
- Safety: All participants who receive at least 1 dose of the study intervention.

6.1.10.1.1 Demographics

Demographic characteristics for all participants in the safety population (through Dose 2) are presented in Table 5. Over half (51.4%) of participants were male. Most participants were White (77.5%), followed by Asian (8.1%), multiracial (7.3%), and Black or African; the minority of participants were Hispanic/Latino (17.0%). The median participant age at study vaccination was 8.0 years of age. The majority of enrollment (85.7%) occurred within U.S. sites. Approximately 90% were baseline SARS-CoV-2 negative and did not have a comorbidity that would increase risk of severe SARS-CoV-2 (73.3%). Obesity was reported in 11.4% of the safety population.

Table 5. Demographic Characteristics, Phase 2/3 Children 5 Years Through 11 Years of Age – Safety Population

Characteristic	Comirnaty (Original monovalent) 10 µg (N[a]=3109) n[b] (%)	Placebo (N[a]=1538) n[b] (%)	Total (N[a]=4647) n[b] (%)
Sex	-	-	-
Male	1609 (51.8)	779 (50.7)	2388 (51.4)
Female	1500 (48.2)	759 (49.3)	2259 (48.6)
Race	-	-	-
White	2402 (77.3)	1199 (78.0)	3601 (77.5)
Black or African American	179 (5.8)	101 (6.6)	280 (6.0)
American Indian or Alaska Native	13 (0.4)	4 (0.3)	17 (0.4)
Asian	258 (8.3)	120 (7.8)	378 (8.1)
Native Hawaiian or other Pacific Islander	10 (0.3)	0	10 (0.2)
Multiracial	235 (7.6)	103 (6.7)	338 (7.3)
Not reported	12 (0.4)	11 (0.7)	23 (0.5)
Ethnicity	-	-	-
Hispanic/Latino	526 (16.9)	265 (17.2)	791 (17.0)
Non-Hispanic/non-Latino	2579 (83.0)	1273 (82.8)	3852 (82.9)
Not reported	4 (0.1)	0	4 (0.1)
Country	-	-	-
Finland	158 (5.1)	81 (5.3)	239 (5.1)
Poland	125 (4.0)	60 (3.9)	185 (4.0)
Spain	162 (5.2)	78 (5.1)	240 (5.2)
USA	2664 (85.7)	1319 (85.8)	3983 (85.7)
Age at vaccination (years)	-	-	-
Mean (SD)	8.0 (1.96)	8.0 (1.97)	8.0 (1.96)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)

Characteristic	Comirnaty (Original monovalent) 10 µg (N[a]=3109) n[b] (%)	Placebo (N[a]=1538) n[b] (%)	Total (N[a]=4647) n[b] (%)
Obese[c]	-	-	-
Yes	352 (11.3)	180 (11.7)	532 (11.4)
No	2754 (88.6)	1358 (88.3)	4112 (88.5)
Missing	3 (0.1)	0	3 (0.1)
Baseline SARS-CoV-2 status	-	-	-
Positive[d]	296 (9.5)	148 (9.6)	444 (9.6)
Negative[e]	2811 (90.4)	1390 (90.4)	4201 (90.4)
Missing	2 (0.1)	0	2 (0.0)
Comorbidities[f]	-	-	-
Yes	829 (26.7)	414 (26.9)	1243 (26.7)
No	2280 (73.3)	1124 (73.1)	3404 (73.3)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 12
Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Dose 1, negative NAAT result at Dose 1, and no medical history of COVID- 19.
f. 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 prespecified comorbidities based on MMWR 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).

Reviewer Comment: The high percentage of individuals with negative baseline SARS-CoV-2 status was likely due to the study enrollment occurring early in the pandemic (March 2021). Demographic characteristics were generally balanced between the Comirnaty (Original monovalent) recipients and placebo recipients, the most being a 1.1% difference in the percentage of females across the study groups.

Demographic characteristics for all Dose 3 recipients in the safety population remained similar to Dose 2 recipients; details are presented in Table 6. The median timing for Dose 3 was 7.9 months post-Dose 2 (range 5.3, 19.4 months). The median follow-up time from Dose 3 to 6 months post-Dose 3 visit or cutoff date was 6.4 months (range 0.3, 13.8 months).

Table 6. Demographic Characteristics – Phase 2/3 – Participants Who Received 3 Doses of Comirnaty (Original monovalent) 10 µg – Safety Population

Characteristic	Comirnaty (Original monovalent) 10 µg (N[a]=2408) n[b] (%)	Placebo then Comirnaty (Original monovalent) 10 µg (N[a]=955) n[b] (%)	Total (N[a]=3363) n[b] (%)
Sex	-	-	-
Male	1216 (50.5)	483 (50.6)	1699 (50.5)
Female	1192 (49.5)	472 (49.4)	1664 (49.5)
Race	-	-	-
White	1837 (76.3)	744 (77.9)	2581 (76.7)
Black or African American	141 (5.9)	64 (6.7)	205 (6.1)
American Indian or Alaska Native	13 (0.5)	4 (0.4)	17 (0.5)
Asian	198 (8.2)	64 (6.7)	262 (7.8)

Characteristic	Comirnaty (Original monovalent) 10 µg (N[a]=2408) n[b] (%)	Placebo then Comirnaty (Original monovalent) 10 µg (N[a]=955) n[b] (%)	Total (N[a]=3363) n[b] (%)
Native Hawaiian or other Pacific Islander	9 (0.4)	0	9 (0.3)
Multiracial	200 (8.3)	73 (7.6)	273 (8.1)
Not reported	10 (0.4)	6 (0.6)	16 (0.5)
Ethnicity	-	-	-
Hispanic/Latino	408 (16.9)	170 (17.8)	578 (17.2)
Non-Hispanic/Non-Latino	1997 (82.9)	785 (82.2)	2782 (82.7)
Not reported	3 (0.1)	0	3 (0.1)
Country	-	-	-
Finland	87 (3.6)	42 (4.4)	129 (3.8)
Poland	86 (3.6)	41 (4.3)	127 (3.8)
Spain	97 (4.0)	44 (4.6)	141 (4.2)
USA	2138 (88.8)	828 (86.7)	2966 (88.2)
Age at vaccination (years)*	-	-	-
Mean (SD)	7.8 (1.84)	7.6 (1.80)	7.8 (1.83)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]	-	-	-
Yes	263 (10.9)	115 (12.0)	378 (11.2)
No	2143 (89.0)	840 (88.0)	2983 (88.7)
Missing	2 (0.1)	0	2 (0.1)
Baseline SARS-CoV-2 status	-	-	-
Positive[d]	222 (9.2)	89 (9.3)	311 (9.2)
Negative[e]	2185 (90.7)	866 (90.7)	3051 (90.7)
Missing	1 (0.0)	0	1 (0.0)
Comorbidities[f]	-	-	-
Yes	634 (26.3)	263 (27.5)	897 (26.7)
No	1774 (73.7)	692 (72.5)	2466 (73.3)

Source: Adapted from STN125742/656, 5_c4591007-interim-6m-12y-6mpd3-report-body.pdf, Table 11
Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD= standard deviation.
Note:* = Age is calculated at first study vaccination.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.
e. Negative N-binding antibody result at Dose 1, negative NAAT result at Dose 1, and no medical history of COVID-19.
f. Number of participants who had at least 1 high-risk underlying condition, based on MMWR 2020;69(32):1081-8 and CDC high-risk underlying conditions list last updated 09FEB2023 and/or obesity (BMI ≥ 95th percentile).

Demographics of participants in the evaluable efficacy population without evidence of infection prior to 7 days post-Dose 2 are presented in Table 7. There were no notable differences in demographic profile across the evaluable efficacy population compared with the safety population. Most participants were not obese (89.2%) and did not have comorbidities (74.2%) associated with an increased risk of severe COVID-19.

Table 7. Demographic Characteristics, Participants Without Evidence of Infection Prior to 7 Days Post-Dose 2 – Blinded Follow-Up Period - Phase 2/3 Children 5 Years Through 11 Years of Age – Evaluable Efficacy Population (2-Dose)

Characteristic	Comirnaty (Original monovalent) 10 µg (N[a]=2703) n[b] (%)	Placebo (N[a]=1348) n[b] (%)	Total (N[a]=4051) n[b] (%)
Sex	-	-	-
Male	1384 (51.2)	688 (51.0)	2072 (51.1)
Female	1319 (48.8)	660 (49.0)	1979 (48.9)
Race	-	-	-
White	2063 (76.3)	1041 (77.2)	3104 (76.6)
Black or African American	149 (5.5)	81 (6.0)	230 (5.7)
American Indian or Alaska Native	13 (0.5)	4 (0.3)	17 (0.4)
Asian	240 (8.9)	115 (8.5)	355 (8.8)
Native Hawaiian or other Pacific Islander	9 (0.3)	0	9 (0.2)
Multiracial	218 (8.1)	96 (7.1)	314 (7.8)
Not reported	11 (0.4)	11 (0.8)	22 (0.5)
Ethnicity	-	-	-
Hispanic/Latino	408 (15.1)	212 (15.7)	620 (15.3)
Non-Hispanic/non-Latino	2291 (84.8)	1136 (84.3)	3427 (84.6)
Not reported	4 (0.1)	0	4 (0.1)
Country	-	-	-
Finland	153 (5.7)	81 (6.0)	234 (5.8)
Poland	81 (3.0)	38 (2.8)	119 (2.9)
Spain	107 (4.0)	64 (4.7)	171 (4.2)
USA	2362 (87.4)	1165 (86.4)	3527 (87.1)
Age at Vaccination	-	-	-
Mean (SD)	8.0 (1.95)	7.9 (1.98)	8.0 (1.96)
Median	8.0	8.0	8.0
Min, max	(5, 11)	(5, 11)	(5, 11)
Obese[c]	-	-	-
Yes	284 (10.5)	149 (11.1)	433 (10.7)
No	2416 (89.4)	1199 (88.9)	3615 (89.2)
Missing	3 (0.1)	0	3 (0.1)
Comorbidities[d]	-	-	-
Yes	695 (25.7)	349 (25.9)	1044 (25.8)
No	2008 (74.3)	999 (74.1)	3007 (74.2)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 13
Abbreviations: BMI = body mass index; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD= standard deviation.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1 visit, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 study visits, and negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID- 19 were included in the analysis.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. 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 prespecified comorbidities based on MMWR 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).

Reviewer Comment*: The demographics of the efficacy population were balanced across the Comirnaty (Original monovalent) and placebo groups. The demographic characteristics for participants with or without evidence of SARS-CoV-2 infection prior to 7 days post-Dose 2 (evaluable efficacy population) and the all-available efficacy*

populations (Dose 1 and Dose 2) were similar to those in the safety population. A quarter of the total population had a comorbidity that put them at increased risk of severe COVID-19 disease.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentages of participants who were obese and who had comorbidities are discussed in Section 6.2.10.1.1.

6.1.10.1.3 Subject Disposition

See section 6.1.10.

Protocol Deviations (PD)
Phase 1: No participants met the reporting criteria for important PDs.
Phase 2/3: PDs during the first two doses were not common but were reported in more Comirnaty (Original monovalent) recipients (3.1%; n=48) than placebo recipients (0.5%; n=4). All but one of the PDs in the Comirnaty (Original monovalent) group (47 [3.1%]) were related to investigational product, but most (38 [2.5%]) due to being unsuitable for use (i.e., Comirnaty (Original monovalent) requires thawing/dilution prior to administration, whereas saline placebo does not). For Dose 3, most of the important PDs in Comirnaty (Original monovalent) recipients were related to concomitant vaccines/medications (15.4%), with "receipt of any other nonstudy coronavirus vaccine at any time prior to or during the study" being the predominant subcategory (15.3%).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Phase 1: There were no primary efficacy or immunogenicity endpoints.

Phase 2/3:
Immunogenicity
The primary endpoint was SARS-CoV-2 50% neutralizing GMT at 1-month post-Dose 2. The ratio of GMTs from children 5 years through 11 years of age (who received the 10-µg dose) compared with young adults 16 years through 24 years of age (who received the 30-µg dose in Study C4591001) was 1.04 (2-sided 95% CI: 0.93, 1.18), which met the 2 success criteria: (1) a GMR point estimate ≥0.8 and (2) a lower bound of the 2-sided 95% CI >0.67 (Table 8).

Table 8. Geometric Mean Titer Ratios – Participants Without Evidence of Infection up to 1-Month post-Dose 2 – Comparison of Children 5 Years Through 11 Years of Age (Immunobridging Subset) to Study C4591001 Young Adults 16 years through 24 Years of Age (Evaluable Immunogenicity Population)

SARS-CoV-2 Neutralization Assay	5-11 Years Comirnaty (Original monovalent) 10 µg (C4591007) n[a] GMT[b] (95% CI[b])	16-24 Years Comirnaty (Original monovalent) 30 µg (C4591001) n[a] GMT[b] (95% CI[b])	5-11 Years/ 16-24 Years GMR[c] (95% CI[c])
NT50 (titer)	264 1197.6 (1106.1, 1296.6)	253 1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 13

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
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). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers ([5 to <12 years] - [16-25 years]) and the corresponding CI (based on the Student t distribution).

Among participants without evidence of SARS-CoV-2 infection up to 1-month post-Dose 2, high and equal percentages (99.2% of both children 5 years through 11 years of age and young adults 16 years through 24 years of age) achieved a seroresponse (defined as achieving a ≥4-fold rise from baseline (before Dose 1) or ≥4 fold increase relative to the LLOQ for those with a baseline measurement below the LLOQ) (Table 9). The percent difference in percentages of seroresponse between the 2 age groups was 0.0% (95% CI: -2.0%, 2.2%) and the lower bound of the 95% CI exceeded the prespecified success margin of -10%.

Table 9. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1-Month Post-Dose 2 – Comparison of Children 5 Years Through 11 Years of Age (Immunobridging Subset) to Study C4591001 Young Adults 16 Years Through 24 Years of Age (Evaluable Immunogenicity Population)

SARS-CoV-2 neutralization Assay	5-11 Years Comirnaty (Original monovalent) 10 µg (C4591007) N[a] % (n[b]) (95% CI[c])	16-24 Years Comirnaty (Original monovalent) 30 µg (C4591001) N[a] % (n[b]) (95% CI[c])	Percent Difference (5-11 Years Minus 16-24 Years)[d] (95% CI[e])
NT50 (titer)	264 99.2 (262) (97.3, 99.9)	253 99.2 (251) (97.2, 99.9)	0.0 (-2.0, 2.2)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 14
Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = SARS-CoV-2 serum neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (5 to <12 years – 16-25 years).
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

> *<u>Reviewer Comment</u>: Effectiveness of Comirnaty (Original monovalent) in children 5 years through 11 years of age is supported by successful immunobridging analyses of GMR and seroresponse rates from a subset of 264 children in Study 1007 compared with 253 young adults 16 years through 24 years of age from Study C4591001.*

6.1.11.2 Analyses of Secondary Endpoints

Phase 1:

Assessment of the 30-µg dose in children was discontinued by the IRC following review of reactogenicity data for this group. Immunogenicity analyses were limited to 15 children who received 10-µg and 15 children who received 20-µg dose without evidence of infection (evaluable immunogenicity population). At 7 days post-Dose 2, both 10 µg and 20 µg elicited similar levels of nAb (Table 10).

Table 10. Geometric Mean Titers 7 days post-Dose 2 – Participants Without Evidence of Infection – Phase 1 –Evaluable Immunogenicity Population

SARS-CoV-2 neutralization Assay	10 µg n[a] GMT[b] (95% CI[b])	20 µg n[a] GMT[b] (95% CI[b])
NT50 (titer)	15 4162.6 (2584.7, 6704.0)	15 4583.4 (2802.9, 7494.8)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 14.22
Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the Visit 3 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visits 1, 2, and 3, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the Visit 3 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
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). Assay results below the LLOQ were set to 0.5 × LLOQ.

Phase 2/3:
Immunogenicity
Similar SARS-CoV-2 neutralizing GMTs were observed for the 264 children 5 years through 11 years of age (1197.6) and 253 young adults 16 years through 24 years of age (1146.5) comprising the immunobridging subset of the evaluable immunogenicity populations (Table 11). Results for the evaluable and all-available immunogenicity populations with or without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 2 were similar to those observed for the evaluable immunogenicity population without prior evidence of infection (data not shown).

Table 11. Geometric Mean Titers – Participants Without Evidence of Infection up to 1-Month Post-Dose 2 – Immunobridging Subset – Phase 2/3 – 5 Years through 11 Years of Age and Study C4591001 Phase 2/3 – 16 Years Through 24 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	Sampling Time Point	5-11 Years Comirnaty (Original monovalent) 10 µg (C4591007) n[a] GMT[b] (95% CI[b])	16-24 Years Comirnaty (Original monovalent) 30 µg (C4591001) n[a] GMT[b] (95% CI[b])	5-11 Years Placebo (C4591007) n[a] GMT[b] (95% CI[b])	16-24 Years Placebo (C4591001) n[a] GMT[b] (95% CI[b])
NT50 (titer)	Pre-Dose 1	264 10.1 (9.9, 10.3)	253 10.3 (9.8, 10.8)	130 10.0 (10.0, 10.0)	45 10.0 (10.0, 10.0)
NT50 (titer)	1-Month Post-Dose 2	264 1197.6 (1106.1, 1296.6)	253 1146.5 (1045.5, 1257.2)	130 10.7 (9.7, 11.8)	45 10.0 (10.0, 10.0)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 14.24

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
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). Assay results below the LLOQ were set to 0.5 × LLOQ.

The GMFRs of SARS-CoV-2 50% serum neutralizing titers from before vaccination to 1-month post-Dose 2 were high (118.2) among participants without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 2. There was a similar magnitude of rise among Comirnaty (Original monovalent) recipients 5 years through 11 years of age compared with 16 years through 24 years of age (Table 12). GMFRs for placebo recipients in both age groups were low. GMFRs for the evaluable and all-available immunogenicity populations without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 2 were similar to those for the evaluable immunogenicity population without prior evidence of infection (data not shown).

Table 12. Geometric Mean Fold Rise From Before Vaccination to 1-Month Post-Dose 2 – Participants Without Evidence of Infection – Immunobridging Subset – Phase 2/3 – 5 Years Through 11 Years of Age and Study C4591001 Phase 2/3 – 16 Years Through 24 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	5-11 Years Comirnaty (Original monovalent) 10 µg (C4591007) n[a] GMFR[b] (95% CI[b])	16-24 Years Comirnaty (Original monovalent) 30 µg (C4591001) n[a] GMFR[b] (95% CI[b])	5-11 Years Placebo (C4591007) n[a] GMFR[b] (95% CI[b])	16-24 Years Placebo (C4591001) n[a] GMFR[b] (95% CI[b])
NT50 (titer)	264 118.2 (109.2, 127.9)	253 111.4 (101.2, 122.7)	130 1.1 (1.0, 1.2)	45 1.0 (1.0, 1.0)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 15
Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N- binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. n = Number of participants with valid and determinate assay results for the specified assay at both pre-vaccination time points and at the given dose/sampling time point.
b. GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Among the total set of participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection (across the combined 2-dose set and 3-dose set), there was an increase in SARS-CoV-2 50% neutralizing titers against the reference strain of SARS-CoV-2 post-Dose 3 compared to pre-Dose 3 (Table 13). The observed GMTs increased from pre-vaccination to 1-month post-Dose 2, waned but remained above pre-vaccination levels, and increased again post-Dose 3. Among 17 participants without prior evidence of infection in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3, the GMTs at 1-month post-Dose 2, pre-Dose 3, and 1-month post-Dose 3 was similar (data not shown).

Table 13. Summary of Geometric Mean Titers – NT50 – Children Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Years Through 11 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	Sampling Time Point[a]	3 Dose Set n[a] GMT[b] (95% CI[b])	2 Dose Set n[a] GMT[b] (95% CI[b])	Total n[a] GMT[b] (95% CI[b])
NT50 (titer)	Pre-Dose 1	79 20.5 (20.5, 20.5)	67 20.5 (20.5, 20.5)	146 20.5 (20.5, 20.5)
NT50 (titer)	1-Month Post-Dose 2	29 1659.4 (1385.1, 1988.0)	67 1110.7 (965.3, 1278.1)	96 1253.9 (1116.0, 1408.9)
NT50 (titer)	Pre-Dose 3	67 271.0 (229.1, 320.6)	-	67 271.0 (229.1, 320.6)
NT50 (titer)	1-Month Post-Dose 3	67 2720.9 (2280.1, 3247.0)	-	67 2720.9 (2280.1, 3247.0)

Source: Adapted from STN125742/656, c4591007-interim-booster-report-body.pdf, Table 11
Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post–Dose 2.
2-Dose immunogenicity set included extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection.
Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
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.

The observed percentage of participants who achieved seroresponse in SARS-CoV-2 50% neutralizing titers at 1-month post-Dose 2 was 100.0% among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection (across the combined 2-dose set and 3-dose set, Table 14). In this population, the observed seroresponse rate waned to 77.6% pre-Dose 3 and then increased to 98.5% 1-month post-Dose 3. Similar seroresponse rates were observed between the 17 participants without prior evidence of SARS-CoV-2 infection in the 3-dose set with assay results at both 1-month post-Dose 2 and at 1-month post-Dose 3 and the larger group (data not shown).

Table 14. Number (%) of Children With Seroresponse – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Years Through 11 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	Sampling Time Point[a]	3 Dose Set N[a] % (n[b]) (95% CI[c])	2 Dose Set N[a] % (n[b]) (95% CI[c])	Total N[a] % (n[b]) (95% CI[c])
NT50 (titer)	1-Month Post-Dose 2	29 100 (29) (88.1, 100.0)	67 100 (67) (94.6, 100.0)	96 100 (96) (96.2, 100.0)
NT50 (titer)	Pre-Dose 3	67	-	67

SARS-CoV-2 Neutralization Assay	Sampling Time Point[a]	3 Dose Set N[a] % (n[b]) (95% CI[c])	2 Dose Set N[a] % (n[b]) (95% CI[c])	Total N[a] % (n[b]) (95% CI[c])
		77.6 (52) (65.8, 86.9)		77.6 (52) (65.8, 86.9)
NT50 (titer)	1-Month Post-Dose 3	67 98.5 (66) (92.0, 100.0)	-	67 98.5 (66) (92.0, 100.0)

Source: Adapted from STN125742/656, c4591007-interim-booster-report-body.pdf, Table 15
Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
Note: 3-Dose immunogenicity set included the first 130 participants received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post–Dose 2. 2-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose 2-evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 timepoint) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 timepoints) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both at baseline (before Dose 1) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.

Efficacy

The first VE hypothesis was evaluated in participants without evidence of prior SARS-CoV-2 infection. In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days post-Dose 2, the observed VE was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days post-Dose 2 to pre-Dose 3 through the blinded follow-up period (Table 15). Vaccine efficacy was demonstrated for participants without evidence of past infection as the predefined success criterion, lower limit of the 95% CI for VE >30%, was met. VE was also analyzed according to first COVID-19 occurrence based on CDC-defined symptoms from 7 days post-Dose 2 (Appendix B). In participants without evidence of infection prior to 7 days post-Dose 2, VE was similar (88.2%; 2-sided 95% CI: 76.9%, 94.5%) to that of the confirmed COVID-19 case analysis described above during the blinded follow-up period prior to Dose 3.

In the evaluable efficacy (2-dose) population with or without evidence of SARS CoV-2 infection prior to 7 days post-Dose 2, the observed VE was 85.7% (2-sided 95% CI: 72.4%, 93.2%) for first COVID-19 cases confirmed from ≥7 days post-Dose 2 to pre-Dose 3 through the blinded follow-up period (Table 15). The first VE hypothesis for participants without evidence of past infection was met, so the second VE hypothesis for participants with or without evidence of past infection was assessed sequentially. VE was demonstrated for participants with and without evidence of past infection as the lower limit of the 95% CI for VE was >30%. VE was also analyzed according to first COVID-19 occurrence based on CDC-defined symptoms from 7 days post-Dose 2. In participants with or without evidence of infection prior to 7 days post-Dose 2, VE was similar (86.0%; 2-sided 95% CI: 73.6%, 93.0%) to that of the confirmed COVID-19 case analysis described above during the blinded follow-up period prior to Dose 3.

Table 15. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days post-Dose 2 to Before Dose 3 – Participants With or Without Evidence of Infection Prior to 7 Days post-Dose 2 – Blinded Follow-Up Period – Phase 2/3 – Evaluable Efficacy (2-Dose) Population

Without Evidence of Infection Prior to 7 Days post-Dose 2 – Blinded Follow-Up Period	Comirnaty (Original monovalent) 10 µg (N[a]=2703) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=1348) Cases n1[b] Surveillance Time[c] (n2[d])	VE (%) (95% CI[e])
Efficacy Endpoint First COVID-19 occurrence from 7 days post-Dose 2 to before Dose 3	10 0.591 (2640)	42 0.292 (1309)	88.2 (76.2, 94.7)
With or Without Evidence of Infection Prior to 7 Days post-Dose 2 – Blinded Follow-Up Period	**(N[a]=3018)**	**(N[a]=1511)**	
Efficacy Endpoint First COVID-19 occurrence from 7 days post-Dose 2 to before Dose 3	12 0.653 (2926)	42 0.292 (1309)	85.7 (72.4, 93.2)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 14 and 15
Abbreviation: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1 visit, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 study visits, and negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID- 19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days post-Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

> ***Reviewer Comment****: VE predefined success criteria were met across the evaluable groups. An exploratory outcome was performed by the Applicant which involved sequencing of the COVID-19 case variants. Delta variants represented 95.2% of the placebo group cases and 70.0% of the Comirnaty (Original monovalent) group cases, with the remainder were Omicron variants (2.4% placebo, 20.0% Comirnaty (Original monovalent)) or Unknown (2.4% placebo, 10.0% Comirnaty (Original monovalent)).*

6.1.11.3 Subpopulation Analyses

GMT

Subgroups of pediatric participants 5 years through 11 years of age and young adults 16 years through 24 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 2) had similar patterns of GMTs from before vaccination to 1-month post-Dose 2 across the Comirnaty (Original monovalent) and placebo groups when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status (data not shown). Several subgroups included a limited number of participants, and their results should be interpreted with caution. There were no meaningful differences in the neutralizing titers based on demographic subgroups within each age group, or between the age groups (C4591007 and C4591001). Participants who were baseline SARS-CoV-2 positive had higher GMTs at both before vaccination and 1-month post-Dose 2 compared with those negative at baseline, in both age groups.

Vaccination with Comirnaty (Original monovalent) induced an increase in GMT at 1-month post-Dose 2 for all participants, irrespective of baseline SARS-CoV-2 status. In the Comirnaty (Original monovalent) group, children from Study 1007 who were baseline SARS-CoV-2 positive (n=21) had GMTs approximately 2.7-fold that of children who were baseline negative (n=273) (3270.0 vs 1211.3). A similar pattern was observed for baseline SARS-CoV-2 positive (n=13) versus negative (n=259) young adults in the Comirnaty (Original monovalent) group from Study C4591001, with baseline positive participants GMTs 1.96-fold that of negative participants (2253.8 vs 1151.2). Notably, the GMTs and fold-increase in GMTs among baseline SARS-CoV-2 positive participants were higher in the pediatric group 5 years through 11 years of age who received Comirnaty (Original monovalent) 10 µg compared with the young adult group 16 years through 24 years of age who received Comirnaty (Original monovalent) 30 µg. Due to the limited number of baseline positive participants in either age group, these differences should be interpreted with caution.

Seroresponse Rate

Seroresponse rates were evaluated by demographic and baseline SARS-CoV-2 status subgroups. Subgroups of pediatric participants 5 years through 11 years of age and young adults 16 years through 24 years of age (with or without prior evidence of SARS-CoV-2 infection up to 1-month post-Dose 2) had similar patterns of seroresponse rates at 1-month post-Dose 2 in the Comirnaty (Original monovalent) group when evaluated by sex, race, ethnicity, and baseline SARS-CoV-2 status. Seroresponse rates in the Comirnaty (Original monovalent) groups had no differences between any subgroups.

Efficacy

In participants without evidence of infection prior to 7 days post-Dose 2, confirmed first cases of COVID-19 and vaccine efficacy were also analyzed by demographic subgroups (Table 16). VE was not meaningfully different by sex, race, ethnicity, country, or comorbidity status. In participants with or without evidence of infection prior to 7 days post-Dose 2, confirmed first cases of COVID-19 and vaccine efficacy were also analyzed by demographic subgroups. VE was not meaningfully different by sex, race, ethnicity, country, or comorbidity status (data not shown).

Table 16. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days post-Dose 2 to Before Dose 3, by Subgroup – Children Without Evidence of Infection Prior to 7 Days post-Dose 2 – Blinded Follow-Up Period – Phase 2/3 – 5 Years Through 11 Years of Age – Evaluable Efficacy (2-Dose) Population

First COVID-19 occurrence from 7 days post-Dose 2 to before Dose 3 Efficacy Endpoint Subgroup	Comirnaty (Original monovalent) 10 µg (N[a]=2703) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=1348) Cases n1[b] Surveillance Time[c] (n2[d])	VE (%) (95% CI[e])
Overall	10 0.591 (2640)	42 0.292 (1309)	88.2 (76.2, 94.7)
Sex	-	-	-
Male	5 0.304 (1351)	24 0.149 (665)	89.8 (72.7, 97.0)
Female	5 0.287 (1289)	18 0.143 (644)	86.1 (61.2, 96.0)
Race	-	-	-
White	8 0.465 (2013)	34 0.232 (1013)	88.3 (74.2, 95.3)

First COVID-19 occurrence from 7 days post-Dose 2 to before Dose 3 Efficacy Endpoint Subgroup	Comirnaty (Original monovalent) 10 µg (N[a]=2703) Cases n1[b] Surveillance Time[c] (n2[d])	Placebo (N[a]=1348) Cases n1[b] Surveillance Time[c] (n2[d])	VE (%) (95% CI[e])
Black or African American	1 0.031 (146)	5 0.017 (77)	89.1 (2.8, 99.8)
Asian	0 0.042 (236)	2 0.022 (115)	100.0 (-174.5, 100.0)
Multiracial	1 0.044 (215)	1 0.018 (90)	58.7 (-3139.5, 99.5)
Ethnicity	-	-	-
Hispanic/Latino	2 0.097 (394)	9 0.052 (205)	88.1 (42.5, 98.7)
Non-Hispanic/non-Latino	8 0.493 (2242)	33 0.241 (1104)	88.2 (73.9, 95.3)
Country	-	-	-
Finland	1 0.069 (146)	5 0.037 (79)	89.2 (3.4, 99.8)
Poland	1 0.034 (80)	4 0.014 (34)	89.5 (-6.1, 99.8)
Spain	1 0.045 (102)	3 0.027 (62)	80.4 (-144.1, 99.6)
USA	7 0.442 (2312)	30 0.214 (1134)	88.7 (73.8, 95.8)
Comorbidities[f]	-	-	-
Yes	2 0.150 (676)	13 0.075 (336)	92.3 (66.0, 99.2)
No	8 0.441 (1964)	29 0.217 (973)	86.4 (69.5, 94.6)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 14.15.
Abbreviation: BMI = body mass index; MMWR = Morbidity and Mortality Weekly Report; NA = not applicable; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 2) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1 visit, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 study visits, and negative NAAT[nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 2) and had no medical history of COVID- 19 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days post-Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. 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 prespecified comorbidities based on MMWR 2020;69(32):1081-8 and/or obesity (BMI ≥ 95th percentile).

Reviewer Comment*: In descriptive analyzes, VE did not vary by subgroup for sex, race, ethnicity, country, or comorbidity status. The VE was similar for those individuals with at least one comorbidity known to increases the risk of severe COVID-19 compared with those individuals without. Some subgroup categories had statistical artifacts, including very wide confidence intervals, due to small sample sizes for some subgroups.*

6.1.11.4 Dropouts and/or Discontinuations

Phase 1: See section 6.1.10.

Phase 2/3: See section 6.1.10. The disposition of pediatric participants 5 years through 11 years of age in the immunobridging subset through 1-month post-Dose 2 was similar to that of all randomized participants for the Comirnaty (Original monovalent) and placebo groups. Most participants across both groups completed the visit at 1-month post-Dose 2 (≥97.7%).

6.1.11.5 Exploratory and Post Hoc Analyses

Severe COVID and Multisystem inflammatory syndrome in children (MIS-C)
Phase 1: There were no participants in any age group that met 1 or more severe COVID-19 illness criteria, and no cases of MIS-C were reported (see definition, Appendix B).

Phase 2/3: Fifteen participants had COVID-19 that met 1 or more severe illness criteria, while no cases of MIS-C were reported (see definition, Appendix B). Criteria for severe illness were fulfilled for 13 cases in the Comirnaty (Original monovalent) group and 2 occurrences in the placebo group (noting 2:1 randomization and shortened surveillance period for placebo group due to unblinding and crossover). All occurrences in the placebo group met protocol-defined severe illness criteria. In the Comirnaty (Original monovalent) group, 10 occurrences met protocol-defined severe illness criteria, 1 case met CDC-defined severe illness criteria, and 2 cases met both severe illness criteria.

6.1.12 Safety Analyses

6.1.12.1 Methods

See section 6.1.7.

6.1.12.2 Overview of Adverse Events

Solicited safety data for Phase 1 are not reported due to small sample size. There were no SAEs, AESIs or deaths among Phase 1 participants. The safety data for Phase 2/3 are reported for the blinded 2 dose series followed by the data following Dose 3.

Phase 2/3 through Dose 2:
The percentages of AEs reported from Dose 1 to 1-month post-Dose 2 were similar for Comirnaty (Original monovalent) recipients and placebo recipients (10.7% vs 9.8%; Table 17). AEs assessed as related by the investigator were reported at a slightly higher frequency by Comirnaty (Original monovalent) recipients (3.5%) compared with placebo recipients (2.1%). Most related AEs were reactogenicity events and in the system organ class (SOC) of general disorders and administration site conditions, reported by 1.6% of Comirnaty (Original monovalent) recipients compared with 1.0% of placebo recipients. The median follow-up time during the original blinded placebo-controlled follow up period from Dose 2 to Dose 3 or cutoff date (May 20, 2022) was 1.9 months (range 0.1, 7.5).

Phase 2/3 post Dose 3:
The percentage of participants reporting any AE was 8.0% in the original Comirnaty (Original monovalent) group (Table 17). The percentage of participants reporting any AEs assessed as related to study intervention by the investigator was 4.0%. The SOC containing the most frequently reported AEs was general disorders and administration site conditions (2.7%), blood and lymphatic system disorders (1.7%), and gastrointestinal disorders (1.3%). Many were reflective of reactogenicity events (e.g., injection site pain, fatigue, pyrexia, headache, nausea, and vomiting). The median follow-up time to six months post-Dose 3 or to study cutoff date (February 28, 2023) was 6.4 months (range 0, 13.8).

Table 17. Overview of AEs – Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 6 months post-Dose 2 or Unblinding and From Dose 3 to 6 months post-Dose 3 – Safety Population

Event	Dose 1 Comirnaty (Original monovalent) N[a]=3096 n[b] (%)	Dose 1 Placebo N[a]=1531-1532 n[b] (%)	Dose 2 Comirnaty (Original monovalent) N[a]=3064 n[b] (%)	Dose 2 Placebo N[a]=1521-1522 n[b] (%)	Dose 3 Comirnaty (Original monovalent) N[a]=2408 n[b] (%)
Solicited injection site reaction within 7 days	2318 (74.9)	526 (34.3)	2241 (73.1)	478 (31.4)	1611 (71.1)
Solicited systemic reaction within 7 days	1506 (48.6)	722 (47.1)	1576 (51.4)	567 (37.3)	1180 (52.1)
Unsolicited non-serious AE within 1 month	--	--	333 (10.7)	150 (9.8)	193 (8.0)
SAEs	--	--	--	--	--
up to 6 months (or unblinding)	--	--	8 (0.3)	2 (0.1)	10 (0.3)
Deaths	0	0	0	0	0

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 18, Table 14.28, and c4591007-interim-mth6-pd3-report-body.pdf, Table 47
Abbreviations: SAEs = serious adverse events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.

Solicited Adverse Reactions:
Local Reactions:
Among Comirnaty (Original monovalent) recipients, pain at the injection site was the most frequently reported local reaction, the frequency was similar post-Dose 1 and post-Dose 2, and the frequency was numerically higher compared to the placebo recipients (Table 18). In Comirnaty (Original monovalent) recipients, the frequencies of redness and swelling were higher post-Dose 2 compared with post-Dose 1 and higher than the placebo recipients. Severe local reactions were reported infrequently (≤0.2%) in the Comirnaty (Original monovalent) and placebo groups after either dose. No Grade 4 local reactions were reported in either group.

The mean duration of pain at the injection site post-Dose 1 was 2.1 days (range 1 to 11 days), for redness 2.0 days (range 1 to 10 days), and for swelling 1.9 days (range 1 to 11 days) for children in the Comirnaty (Original monovalent) 10 µg group. The mean duration of pain at the injection site post- Dose 2 was 2.3 days (range 1 to 37 days), for redness 2.0 days (range 1 to 10 days), and for swelling 2.2 days (range 1 to 16 days) for children in the Comirnaty (Original monovalent) 10 µg group in the blinded placebo-controlled follow-up period up to the cutoff date of May 20, 2022.

Table 18. Frequency and Percentages of Children With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Blinded Placebo-Controlled Follow-Up Period – Children 5 Years Through 11 Years of Age – Safety Population

	Comirnaty (Original monovalent) Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531-1532 n[b] (%)	Comirnaty (Original monovalent) Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521-1522 n[b] (%)
Redness[c]	-	-	-	-
Any (≥0.5 cm)	434 (14.0)	91 (5.9)	575 (18.8)	79 (5.2)
Mild	287 (9.3)	78 (5.1)	315 (10.3)	57 (3.7)
Moderate	146 (4.7)	11 (0.7)	257 (8.4)	20 (1.3)
Severe	1 (0.0)	2 (0.1)	3 (0.1)	2 (0.1)
Swelling[c]	-	-	-	-
Any (≥0.5 cm)	320 (10.3)	46 (3.0)	450 (14.7)	41 (2.7)
Mild	177 (5.7)	28 (1.8)	247 (8.1)	30 (2.0)
Moderate	142 (4.6)	18 (1.2)	203 (6.6)	11 (0.7)
Severe	1 (0.0)	0	0	0
Pain at the injection site[d]	-	-	-	-
Any	2258 (72.9)	482 (31.5)	2181 (71.2)	434 (28.5)
Mild	1810 (58.5)	434 (28.3)	1642 (53.6)	389 (25.6)
Moderate	442 (14.3)	48 (3.1)	533 (17.4)	44 (2.9)
Severe	6 (0.2)	0	6 (0.2)	1 (0.1)
Any local reaction[e]	2318 (74.9)	526 (34.3)	2241 (73.1)	478 (31.4)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 14.28
Note: Reactions were collected in the e-diary and at unscheduled clinical assessments from Day 1 through Day 7 after each vaccination.
Note: Grade 4 reactions were classified by the investigator or medically qualified person.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: ≥0.5 to <2.0 cm; Moderate: >2.0 to <7.0 cm; Severe: >7.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.
e. Any local reaction: any redness ≥0.5 cm, any swelling ≥0.5 cm, or any pain at the injection site.

Dose 3 was administered unblinded and without a placebo comparator. The frequencies of any local reaction (redness, swelling, or pain at the injection site) within 7 days post-Dose 3 was 71.1%. Pain at the injection site was the most frequently reported local reaction (69.2%), followed by redness (15.6%), and swelling (12.6%). Most local reactions reported by Comirnaty (Original monovalent) recipients were mild or moderate in severity. Severe local reactions of pain at the injection site or redness were reported infrequently after any dose (0.5% and 0.2%, respectively), and there were no reported severe local reactions of swelling. No Grade 4 local reactions were reported at any dose. The median time to onset for local reactions after receiving Comirnaty (Original monovalent) occurred on Day 1.0 post-Dose 3, and all reactions resolved within a median duration of 1 to 3 days.

Systemic Reactions:
Systemic events were reported by Comirnaty (Original monovalent) recipients at higher frequencies and severity for Dose 2 compared with Dose 1 for most events, with the exceptions of vomiting and diarrhea (Table 19). The most frequently reported systemic event was fatigue followed by headache.
Most systemic events were reported less frequently in placebo recipients compared with Comirnaty (Original monovalent) recipients. Most systemic events were mild or moderate in severity. Severe systemic events were infrequent (≤0.9%).

Two Comirnaty (Original monovalent) recipients had a fever >40°C:

- One (1) participant reported a fever of 40.1°C on Day 2 post-Dose 1 (also reported as an AE of pyrexia) and returned to normal body temperature (37.1°C) the next day. This participant also had an AE of neutropenia on Day 3 post-Dose 1. This participant withdrew from the study and did not receive Dose 2.
- One (1) participant reported a fever of 40.3°C on Day 3 post-Dose 2 and returned to normal body temperature (37.1°C) the next day. This participant did not have any concurrent AEs reported.

The mean duration for all systemic events after receiving Comirnaty (Original monovalent) or placebo was 1 to 2.6 days post-Dose 1 or Dose 2 (range 1 to 119).

Table 19. Frequency and Percentages of Participants With Solicited Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Blinded Placebo-Controlled Follow-Up Period – Children 5 Years Through 11 Years of Age – Safety Population

	Comirnaty (Original monovalent) Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531-1532 n[b] (%)	Comirnaty (Original monovalent) Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521-1522 n[b] (%)
Fever	-	-	-	-
≥38.0°C	64 (2.1)	21 (1.4)	193 (6.3)	21 (1.4)
≥38.0°C to 38.4°C	37 (1.2)	10 (0.7)	101 (3.3)	13 (0.9)
>38.4°C to 38.9°C	22 (0.7)	9 (0.6)	70 (2.3)	5 (0.3)
>38.9°C to 40.0°C	4 (0.1)	2 (0.1)	21 (0.7)	3 (0.2)
>40.0°C	1 (0.0)	0	1 (0.0)	0
Fatigue[c]	-	-	-	-
Any	1067 (34.5)	496 (32.4)	1200 (39.2)	383 (25.2)
Mild	702 (22.7)	323 (21.1)	665 (21.7)	230 (15.1)
Moderate	360 (11.6)	171 (11.2)	508 (16.6)	149 (9.8)
Severe	5 (0.2)	2 (0.1)	27 (0.9)	4 (0.3)
Headache[c]	-	-	-	-
Any	703 (22.7)	372 (24.3)	870 (28.4)	284 (18.7)
Mild	530 (17.1)	275 (18.0)	576 (18.8)	201 (13.2)
Moderate	170 (5.5)	91 (5.9)	286 (9.3)	82 (5.4)
Severe	3 (0.1)	6 (0.4)	8 (0.3)	1 (0.1)
Chills[c]	-	-	-	-
Any	174 (5.6)	84 (5.5)	301 (9.8)	66 (4.3)
Mild	138 (4.5)	69 (4.5)	205 (6.7)	52 (3.4)
Moderate	36 (1.2)	15 (1.0)	94 (3.1)	13 (0.9)
Severe	0	0	2 (0.1)	1 (0.1)
Vomiting[d]	-	-	-	-
Any	63 (2.0)	30 (2.0)	62 (2.0)	27 (1.8)
Mild	52 (1.7)	28 (1.8)	56 (1.8)	22 (1.4)
Moderate	11 (0.4)	2 (0.1)	5 (0.2)	5 (0.3)
Severe	0	0	1 (0.0)	0
Diarrhea[e]	-	-	-	-
Any	198 (6.4)	75 (4.9)	166 (5.4)	76 (5.0)
Mild	184 (5.9)	72 (4.7)	149 (4.9)	70 (4.6)
Moderate	14 (0.5)	3 (0.2)	15 (0.5)	6 (0.4)
Severe	0	0	2 (0.1)	0

	Comirnaty (Original monovalent) Dose 1 N[a]=3096 n[b] (%)	Placebo Dose 1 N[a]=1531-1532 n[b] (%)	Comirnaty (Original monovalent) Dose 2 N[a]=3064 n[b] (%)	Placebo Dose 2 N[a]=1521-1522 n[b] (%)
New or worsened muscle pain[c]	-	-	-	-
Any	289 (9.3)	126 (8.2)	368 (12.0)	104 (6.8)
Mild	206 (6.7)	96 (6.3)	245 (8.0)	68 (4.5)
Moderate	82 (2.6)	30 (2.0)	122 (4.0)	36 (2.4)
Severe	1 (0.0)	0	1 (0.0)	0
New or worsened joint pain[c]	-	-	-	-
Any	106 (3.4)	70 (4.6)	159 (5.2)	57 (3.7)
Mild	71 (2.3)	56 (3.7)	103 (3.4)	42 (2.8)
Moderate	35 (1.1)	14 (0.9)	56 (1.8)	15 (1.0)
Any systemic event[f]	1506 (48.6)	722 (47.1)	1576 (51.4)	567 (37.3)
Antipyretic or pain medication use[g]	436 (14.1)	135 (8.8)	601 (19.6)	111 (7.3)

Source: Adapted from STN125742/656, c4591007-interim-mth6-pd2-report-body.pdf, Table 14.42
Note: Events and use of antipyretic or pain medication were collected in the e-diary and at unscheduled clinical assessments from Day 1 through Day 7 after each dose. Grade 4 events were classified by the investigator or medically qualified person.
a. N = number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified characteristic.
c. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity;
Grade 4: emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain.
d. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration; Grade 4: emergency room visit or hospitalization for severe vomiting.
e. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours; Grade 4: emergency room visit or hospitalization for severe diarrhea.
f. Any systemic event: any fever ≥38.0℃, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
g. Severity was not collected for use of antipyretic or pain medication.

The frequency of any systemic event within 7 days post-Dose 3 was 52.1%. Fatigue (39.6%) was the most frequently reported systemic event within 7 days post-Dose 3, followed by headache (26.9%), new or worsened muscle pain (15.5%), chills (10.2%), fever (6.8%), new or worsened joint pain (5.7%), diarrhea (4.6%), and vomiting (2.7%). One participant reported fever>40.0°C post-Dose 3. Antipyretic or pain medication use after any dose was reported by 27.9% of participants post-Dose 3. Most systemic events were mild or moderate. Severe systemic events were infrequent (≤2.1%). Besides the one temperature >40°C, no Grade 4 systemic events were reported post-Dose 3. Median time to onset for systemic events after receiving Dose 3 occurred on Day 2.0, and all events resolved with a median duration of 1.0 day.

Immediate AEs:
Post-Dose 1, the frequency of immediate AEs was 0.2% in both groups. Immediate AEs reported post-Dose 1 were predominantly injection site pain, reported in 5 participants (0.1%) followed by injection site erythema, injection site urticaria, vessel puncture site erythema and procedural vomiting.

Post-Dose 2, immediate AEs were reported by 0.2% of Comirnaty (Original monovalent) recipients and 0.1% of placebo recipients. These AEs included injection site pain, nausea, injection site erythema, and fatigue. No allergic AEs were reported after either dose of Comirnaty (Original monovalent) within 30 minutes after vaccination.

Post-Dose 3, immediate AEs were low in frequency (0.3%). Immediate AEs reported post-Dose 3 were predominantly injection site pain (0.2%), followed by injection site erythema, injection site urticaria, vessel puncture site erythema, and pruritis.

Unsolicited Adverse Events:
The frequency of AEs reported from Dose 1 to 1-month post-Dose 2 during the blinded placebo-controlled follow-up period was a little higher in the Comirnaty (Original monovalent) (10.7%) compared with placebo (9.8%) recipients. Many of the AEs were reflective of reactogenicity events that were reported as AEs (i.e., headache, vomiting, and injection site pain). AE frequencies in these reactogenicity SOCs (Comirnaty (Original monovalent) vs placebo) were:

- general disorders and administration site conditions: 2.1% vs 1.9%
- gastrointestinal disorders: 1.3% vs 1.6%
- nervous system disorders: 0.7% vs 0.6%
- musculoskeletal and connective tissue disorders: 0.5% vs 0.6%.

Aside from SOCs that reflect events consistent with reactogenicity, other categories of events were consistent with events that would be expected in a general population of children in this age group and/or showed no imbalance between the vaccine and placebo groups.

The frequency of AEs reported from Dose 3 to 1-month post-Dose 3 was 8.0%. The SOC containing the most frequently reported AEs in the Comirnaty (Original monovalent) group was general disorders and administration site conditions (2.7%), blood and lymphatic system disorders (1.7%), and gastrointestinal disorders (1.3%). Many of the AEs were reflective of reactogenicity events that were reported as AEs (e.g., injection site pain, fatigue, pyrexia, headache, nausea, and vomiting) or are commonly reported for this age group (e.g., oropharyngeal pain, rhinorrhea, falls). In the blood and lymphatic system disorders SOC, 39 participants (1.6%) reported lymphadenopathy.

> ***Reviewer Comment****: There was one participant who reported a headache that resolved after 119 days post-vaccination. This represents a single case out of the total participants who reported headaches, constituting <0.1% of all headache events in the study. The 119-day duration is clinically inconsistent with known vaccine reactogenicity, and the extended duration suggests an alternative etiology likely unrelated to vaccination.*

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

From Dose 1 to unblinding date or Dose 3, severe AEs were reported by 8 (0.3%) Comirnaty (Original monovalent) recipients and 2 (0.1%) placebo recipients. Only one SAE was classified as related to the intervention (Comirnaty (Original monovalent) by the investigator (a transient ischemic attack described below). In the Comirnaty (Original monovalent) group SAEs included:

- One participant had a Grade 3 SAE of transient ischemic attack (TIA) with onset on Day 113 post-Dose 2 (duration 7 days) that was considered by the investigator as related to study intervention but considered unrelated by the Applicant.
- One participant had a Grade 3 SAE of bacterial arthritis (left knee septic arthritis) with onset on Day 15 post-Dose 1 (duration 45 days) that the investigator unrelated to study intervention.

- An SAE of epiphyseal fracture (proximal radius Salter Harris 2 fracture) of Grade 3 severity with onset on Day 20 post-Dose 1 (duration 32 days) that the investigator considered unrelated to study intervention.
- One participant had a Grade 3 SAE of pneumonia respiratory syncytial viral with onset on Day 49 post-Dose 2 (duration of 31 days) that the investigator considered unrelated to study intervention.
- A Grade 3 SAE of cellulitis (cellulitis in right forearm) was reported on Day 154 post-Dose 2 (duration 14 days). The investigator considered the event as unrelated to study intervention.
- A Grade 3 SAE of testicular appendage torsion was reported on Day 101 post-Dose 2 (duration 2 days). The investigator considered the event unrelated to study intervention.

In the placebo group, two SAEs were reported:

- Grade 3 events of abdominal pain and pancreatitis (noted as occurring 'post-injury') both reported in 1 participant as SAEs that the investigator unrelated to study intervention.
- A Grade 3 SAE of complicated appendicitis was reported on Day 121 post-Dose 2 (duration 4 days). The investigator considered the event unrelated to study intervention.

From Dose 3 to 6 months post-Dose 3, 10 (0.4%) Comirnaty (Original monovalent) recipients reported at least 1 SAE, and none of the SAEs were assessed as related to the study intervention by the investigator.

> ***Reviewer Comment****: Participant narratives were reviewed for these SAEs, and this reviewer concurs with the investigator assessment of relatedness with one exception. One participant experienced a TIA 113 days post-Dose 2. While the investigator assessed this as related to vaccination, both the Applicant and this reviewer consider it unrelated to the vaccine based on the temporal distance from vaccination, uncertain diagnosis, and rarity of TIA in pediatric populations.*

6.1.12.5 Adverse Events of Special Interest (AESI)

No cases of anaphylaxis, myocarditis/pericarditis, Bell's palsy (or facial paralysis/paresis), or appendicitis were reported in Comirnaty (Original monovalent) recipients. Based on previous FDA requests for information on AEs of clinical interest in prior submissions, the following MedDRA Standardized MedDRA Queries (SMQ) were applied to search the safety data: Angioedema, Arthritis, Convulsions, Demyelination, Hypersensitivity, Peripheral Neuropathy, and Vasculitis. AEs of clinical interest that were identified in the safety database from Dose 1 to unblinding (before Dose 3) are summarized here:

- Lymphadenopathy - 27 (0.9%) Comirnaty (Original monovalent) recipients and 4 (0.3%) placebo recipients reported AEs of lymphadenopathy (including lymphadenopathy, lymph node pain, axillary pain, and injection site lymphadenopathy). All events were mild in severity and were considered to be related to study intervention. Most events had a median time to onset of 3.0 days post-Dose 1 and 2.0 days post-Dose 2. The median duration of most events was 3.5 days.
- Rash (including pruritic, macular, maculo-papular, erythematous, and injection site rash) - reported in 17 (0.5%) Comirnaty (Original monovalent) recipients and 6 (0.4%) placebo recipients. Twelve Comirnaty (Original monovalent) recipients had rashes that the investigator considered to be related to study intervention; most of these were Grade 1 (2 participants with Grade 2), typically had an onset within 7 days post-vaccination. *Henoch-Schönlein Purpura (HSP)*: 1 Comirnaty (Original monovalent) recipient reported an AE of HSP (mild in severity) on Day 21 post-Dose 1, which resolved within 15 days.

The event was assessed by the investigator as unrelated to study intervention; however, the participant did not receive Dose 2.

- Hypersensitivity – no cases were reported for Comirnaty (Original monovalent) recipients. Two placebo recipients reported hypersensitivity, and 1 placebo recipient reported an AE of drug hypersensitivity.
- Arthritis – no events were reported that were considered as related to study vaccination.
- Convulsions – no cases were reported during the blinded placebo-controlled follow-up period from Dose 1 to unblinding. During the open-label follow-up period from unblinding to data cutoff date, no cases of convulsions were reported for original Comirnaty (Original monovalent) recipients. One original placebo recipient reported an event of *petit mal* epilepsy (absence seizures) of moderate severity on Day 8 after receiving Dose 1 of Comirnaty (Original monovalent), which was reported as continuing at the time of data cutoff date. The event was considered by the investigator as unrelated to study intervention and cause of the event was reported as neurologic disorder. This participant received both doses of Comirnaty (Original monovalent) after unblinding.
- Paresthesia – one related case of paresthesia (bilateral lower extremity tingling) was reported in one Comirnaty (Original monovalent) recipient (White, non-Hispanic/non-Latino 9-year-old female) during the blinded placebo-controlled follow-up period from Dose 1 to unblinding. Onset was 1-day post-Dose 2 and reported as recovered/resolved within 3 days.
- Tic – a psychiatric disorder event of tic was reported in 1 Comirnaty (Original monovalent) recipient (White, non-Hispanic/non-Latino 9-year-old male) during the blinded placebo-controlled follow-up period from Dose 1 to unblinding. This was reported as a Grade 3 tic with onset at 7 days post-Dose 2. The AE was considered by the investigator as related to study intervention and led to unblinding of the participant post-Dose 2. This participant reported no medical history, no other AEs or any severe reactogenicity events, and received no prohibited concomitant treatments or nonstudy vaccines. He was evaluated by his primary care physician within approximately 1 week following tic onset; an MRI performed another 1 week later did not reveal any pathology. A pediatric neurologist was consulted but no specific diagnosis was given, and a change in lifestyle was recommended. The neurologist did not consider the new tic to be to the vaccine.
- Severe COVID-19 - no severe COVID-19 cases were reported.
- MIS-C - no MIS-C cases were reported.

There were several AESIs (reported between Dose 3 and Data Cutoff Date (February 28, 2023) considered related to vaccine: 1 event of urticaria and 3 events of rash. Lymphadenopathy was reported in 59 Comirnaty (Original monovalent) recipients, with a median time-to-onset of 2 days following Dose 3. Median duration was 5.0 days.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations related to safety were not performed in this study.

6.1.12.7 Dropouts and/or Discontinuations

Two AEs leading to withdrawal were reported in a Comirnaty (Original monovalent) recipient, a 5-year-old Asian, non-Hispanic/non-Latino female with a history of gingivitis and benign transient neutropenia with a baseline absolute neutrophil count of 480. On Day 2 post-Dose 1, she developed a Grade 3 fever of 40.1°C, which resolved the same day after receiving Tylenol. On Day 3 post-Dose 1, the participant had a planned hematology appointment in follow-up to the benign neutropenia diagnosis. Routine laboratory tests were completed; complete blood

count (CBC) showed white blood cells (WBC) 2.26, hemoglobin/hematocrit (H/H) 11.2/33, platelets 267, and absolute neutrophil count (ANC) 20. No other symptoms or infections were reported at that time. On Day 19, the investigator was contacted by the caregiver who reported the participant having one week of bleeding gums. On Day 23, a follow up CBC was completed which showed WBC 2.78, H/H 12.1/37.6, platelets 299, and ANC improved to 70. The participant did not receive treatment other than routine mouth washing. The parent withdrew the participant from the study intervention on Day 23 (i.e., did not receive Dose 2) because of the pyrexia and neutropenia. She remained in the study to be evaluated for safety, immunogenicity, and/or efficacy. In the opinion of the investigator, the pyrexia and neutropenia were related to the study intervention.

There were no AEs leading to withdrawal reported between Dose 3 and data cutoff point (February 28, 2023).

6.1.13 Study Summary and Conclusions

Efficacy

- In the evaluable efficacy (2-dose) population without evidence of SARS-CoV-2 infection prior to 7 days post-Dose 2, the observed VE was 88.2% (2-sided 95% CI: 76.2%, 94.7%) for first COVID-19 cases confirmed from ≥7 days post-Dose 2 to before Dose 3 through the blinded follow-up period.
- Most of the COVID-19 cases in this VE analysis accrued from summer 2021 through autumn 2021, during a time the Delta variant was circulating in the US and globally. This was confirmed by next-generation sequencing which showed that most cases in the Comirnaty (Original monovalent) and placebo recipients were of the Delta variant lineage. This VE analysis captures the earliest stages of the first global Omicron variant wave.
- Subgroup analyses did not identify any clinically meaningful differences in efficacy parameters; however, some subgroups had small sample sizes. Taken together, these results demonstrate that a 2-dose series of Comirnaty (Original monovalent) 10 µg provided protection against COVID-19 in children 5 years through 11 years of age during the peak Delta variant wave.
- There was no post-Dose 3 efficacy evaluation, but immunogenicity data were reported for 67 children without evidence of SARS-CoV-2 infection. The neutralizing titers against the wild-type variant of SARS-CoV-2 observed 1-month post-Dose 3 increased by over 2-fold (2720.9) compared with those from 1-month post-Dose 2 (1253.9) and approximately 10-fold from pre-Dose 3 vaccination (271.0), with a GMR of 2.17 for participants with available titers 1-month post-Dose 3 compared with those with available titers from 1-month post-Dose 2 (2-sided 95% CI: 1.76, 2.68). The observed proportion of participants who achieved seroresponse (i.e., ≥4-fold rise in SARS-CoV-2 neutralizing titers from pre-Dose 1, or ≥4 × LLOQ for a pre-Dose 1 measurement <LLOQ) was 100.0% at 1-month post-Dose 2, waned by pre-Dose 3 to 77.6%, and increased to 98.5% at 1-month post-Dose 3. The difference in seroresponse percentages at 1-month post-Dose 3 compared with at 1-month post-Dose 2 was -1.5% (2-sided 95% CI: -8.0%, 2.4%).

Safety

Reactogenicity Profile

The reactogenicity profile after 10 µg of Comirnaty (Original monovalent) in children 5 years through 11 years of age was mild to moderate, with most events arising within the first 1 to 2 days after dosing. The most common local reaction after any dose was injection site pain, which

was reported at a similar frequency after either dose. The mean duration of local reactions was 1.9 to 2.1 days. The most common systemic reactogenicity events included fatigue, headache, muscle pain, and chills, which were reported slightly more frequently post-Dose 2 than post-Dose 1. The mean duration of systemic reactions was 1 to 2.6 days. The frequency of severe systemic events after any dose was low. Subgroup analyses of reactogenicity suggested no major differences based on participant demographics or baseline SARS-CoV-2 status.

Adverse Event Profile
Most AEs in children 5 years through 11 years of age were due to local and systemic reactogenicity, with low incidences of related or severe events. The median duration of AEs was 3.5 to 5 days. Few SAEs and AEs (2 in the same participant) led to study withdrawal. Review of AEs, SAEs, and AEs of clinical interest did not reveal any short-term safety concerns after administration of Comirnaty (Original monovalent) 10 µg. Subgroup analyses of AEs did not reveal any major differences based on participant demographics or baseline SARS-CoV-2 status.

No cases of myocarditis/pericarditis or anaphylaxis were reported post-vaccination through the data cutoff date (May 30, 2022). Rashes considered related to vaccine were reported in 0.4% of participants in the Comirnaty (Original monovalent) group; they were mild to moderate in severity.

Lymphadenopathy has been associated with the vaccine and was observed during the 2-dose primary series across age groups in these studies. The incidence of lymphadenopathy (0.9% in the blinded placebo-controlled follow-up period) was similar to that observed in Phase 2/3 AE analyses for adolescents 12 years through 15 years of age (0.8%). These events were typically mild and self-limited.

6.2 C4591048 Substudy D (Study 1048 SSD)

NCT05543616: “A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Variant-Adapted BNT162b2 RNA-Based Vaccine Candidate(s) in Healthy Children.”

Study Overview: Study 1048 SSD evaluated the safety, tolerability, and immunogenicity of a fourth dose (second booster) of the BNT162b2 (Bivalent Original and BA.4/BA.5) COVID-19 vaccine 10 µg in children 5 years through 11 years of age. The study began on September 23, 2022 (first participant first visit), with a data cutoff date of August 17, 2023.

> ***Reviewer Comment****: The study enrolled 3 groups (see details in subsection 6.2.10). However, enrollment to Groups 1 and 3 were terminated due to enrollment delays after issuance of an EUA for BNT162b2 (Bivalent Original and BA.4/BA.5) and by the subsequent EUA for Comirnaty (Monovalent XBB.1.5). The focus of the review is on Group 2 because enrollment numbers for the other 2 groups were small.*

6.2.1 Objectives (Primary, Secondary)

Primary Safety: To describe the safety and tolerability profile of prophylactic BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg given as a fourth dose in children 5 years through 11 years of age.

Endpoints: Local reactions for up to 7 days following study vaccination (pain at the injection site, redness, and swelling); Systemic events for up to 7 days following study vaccination (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new

or worsened joint pain); Adverse events (AEs) from the study vaccination through 1 month after the study vaccination; Serious adverse events (SAEs) from the study vaccination through 6 months after the study vaccination

Primary Immunogenicity: To descriptively compare the anti-Omicron BA.4/BA.5 immune response between children 5 years through 11 years of age who received 3 prior doses of Comirnaty (Original monovalent) 10 µg and received bivalent BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg as a fourth dose in Group 2 and Study C4591007 Phase 2/3 children 5 years through 11 years of age who received 3 doses of Comirnaty (Original monovalent) 10 µg.

Endpoints: In children complying with the key protocol criteria (evaluable participants):

- Geometric mean ratio (GMR), the ratio of the geometric mean of SARS-CoV-2 Omicron BA.4/BA.5–neutralizing titers at 1-month post-Dose 4 for children who received 3 prior doses of Comirnaty (Original monovalent) 10 µg and a fourth dose of BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg to those at 1-month post-Dose 3 for Study C4591007 Phase 2/3 children who received 3 doses of Comirnaty (Original monovalent) 10 µg
- The difference in percentage of children with seroresponse to the Omicron BA.4/BA.5 strain between children who received 3 prior doses of Comirnaty (Original monovalent) 10 µg and a fourth dose of bivalent BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg at 1-month post-Dose 4 and Study C4591007 Phase 2/3 children who received 3 doses of Comirnaty (Original monovalent) 10 µg at 1-month post-Dose 3

Secondary Immunogenicity: To describe the immune response elicited by BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg given as a fourth dose.

Endpoints: In children complying with the key protocol criteria (evaluable participants), for each strain-specific neutralizing titer:

- GMTs at each time point
- GMFR from before study vaccination to each subsequent time point
- Percentages of children with seroresponse at each time point following vaccination

6.2.2 Design Overview

Study C4591048 Substudy D was an open-label study designed to evaluate the safety, tolerability, and immunogenicity of a third or fourth dose of BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg in children 5 years through 11 years of age.

Approximately 250 children were targeted for enrollment across 3 groups. However, when BNT162b2 (Bivalent Original and BA.4/BA.5) became publicly available to children 5 years through 11 years of age as a third dose under the November 2022 and April 2023 EUA amendments, respectively, enrollment in Groups 1 and 3 slowed. The Applicant terminated enrollment into Groups 1 and 3 in Protocol Amendment 3 (August 1, 2023) following FDA's recommendation for an update to the COVID-19 vaccine composition to target the Omicron XBB.1.5 strain and subsequent withdrawal of EUA for the BNT162b2 (Bivalent Original and BA.4/BA.5).

6.2.3 Population

Study 1048 SSD enrolled children 5 years through 11 years of age who were in good health and had previously received 2 or 3 doses of Comirnaty (Original monovalent) 10 µg, with the last dose administered ≥90 days prior to enrollment. A subset of children (Group 3) was previously enrolled in Study 1007.

Key Inclusion Criteria:

- Healthy children aged 5 years through 11 years at the time of enrollment
- Previously received 2 or 3 doses of Comirnaty (Original monovalent) 10 µg
- Last dose administered ≥90 days prior to enrollment

Key Exclusion Criteria:

- Presence of a medical or psychiatric condition, including recent (within the past 12 months) or active suicidal ideation or behavior
- 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
- Prior or current receipt of any COVID-19 vaccine other than Comirnaty/BNT162b2
- Use of medications intended to prevent COVID-19
- Receipt of immunosuppressant medications, blood products, immunoglobulin, or monoclonal antibodies (except palivizumab) within 60 days prior to enrollment

6.2.4 Study Treatments or Agents Mandated by the Protocol

Intervention name: BNT162b2 (Bivalent Original and BA.4/BA.5) manufactured by BioNTech
Dose: 10 µg (Comirnaty (Original monovalent) 5 µg and BNT162b2 Omicron [B.1.1.529 sublineage BA.4/BA.5] 5 µg)
Route of administration: Intramuscular (IM) injection
Schedule: Single dose (fourth dose overall for Groups 2 and 3, third dose overall for Group 1)
Lot number: PA2845884/P233021-0002L (Pfizer)
Diluent: 0.9% Sodium Chloride Injection, USP • Lot number: FK8454 • Manufacturer: Pfizer
The study vaccine was supplied as a frozen concentrated liquid that required dilution with sterile 0.9% Sodium Chloride Injection, USP prior to use.

6.2.5 Directions for Use

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

6.2.6 Sites and Centers

The substudy was conducted at 10 sites in the US.

6.2.7 Surveillance/Monitoring

Study oversight included Institutional Review Board/Independent Ethics Committee review and approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents. The study was monitored by ICON (a clinical research organization) with regular site visits to ensure adherence to the protocol, compliance with GCP, and completeness, accuracy, and consistency of the data.

Safety Assessments:

- Immediate adverse events (AEs) for 30 minutes post-Dose 3 or post-Dose 4 vaccination
- Solicited local and systemic adverse reactions (ARs) for up to 7 days following study vaccination (starting on the day of vaccination and followed by 6 subsequent days). Solicited ARs were recorded using electronic diaries (e-diaries) as follows:

    - Solicited local ARs: pain at the injection site, redness, and swelling
    - Solicited systemic ARs: fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain
- Unsolicited adverse events (AEs) from the study vaccination through 1 month after the study vaccination
- Serious adverse events (SAEs) from the study vaccination through 6 months after the study vaccination
- Adverse events of special interest (AESIs), including myocarditis and pericarditis, through 6 months after the study vaccination

Immunogenicity Assessments:
Blood samples were collected at baseline (Day 1, pre-vaccination) and Day 30 (1 month post-vaccination) for immunogenicity assessments measuring the following:

1. SARS-CoV-2 neutralization assay (reference strain): Validated SARS-CoV-2 neutralization assay to determine reference strain-specific neutralizing titers, reported as 50% neutralizing titer (NT50)
2. SARS-CoV-2 neutralization assay (Omicron BA.4/BA.5): Validated SARS-CoV-2 neutralization assay to determine Omicron BA.4/BA.5-specific neutralizing titers, reported as NT50
3. Baseline SARS-CoV-2 status: Evaluated using SARS-CoV-2 RT-PCR assay and N-binding antibody assay to detect anti-SARS-CoV-2 nucleocapsid protein antibodies

6.2.8 Endpoints and Criteria for Study Success

Please see Section 6.2.1.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The sample size was not based on formal hypothesis testing. Confidence intervals for all endpoints were presented as 2-sided at the 95% level unless specified otherwise. All immunogenicity analyses were descriptive and based on the evaluable immunogenicity population.

Immunogenicity Analyses: Descriptive analyses were performed to characterize Omicron BA.4/BA.5 and reference strain neutralization responses.

- GMTs and GMFRs with 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and fold rises, respectively, and the corresponding CIs (based on Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ
- GMR and associated 95% CIs were calculated by exponentiating the difference in LS means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model that includes the baseline neutralizing titer, postbaseline infection status, and vaccine group as covariates.
- Seroresponse was defined as achieving a ≥4-fold rise from baseline (before the study vaccination [fourth dose]) for children in Group 2 of Substudy D. If the baseline measurement was below the LLOQ, seroresponse was defined by post-vaccination measure of ≥4 × LLOQ. For the comparator group from Study C4591007 Phase 2/3, seroresponse was defined as achieving a ≥4-fold rise prior to Dose 3. If the pre-third dose measurement was below the LLOQ, seroresponse was defined by post-vaccination measure of ≥4 × LLOQ.

To account for potential confounders, the comparators for Group 2 from Study C4591007 were matched by age and prior SARS-CoV-2 infection status.

Safety analyses: Safety analyses were descriptive and were conducted for the safety population. AEs and SAEs were categorized according to MedDRA terms. Counts, percentages, and associated Clopper-Pearson 95% CIs of reactogenicity, AEs, and SAEs were provided.

6.2.10 Study Population and Disposition

The substudy enrolled a total of 136 children 5 years through 11 years of age who had previously received original Comirnaty (Original monovalent) 10 µg representing three distinct groups.
Group 1: Two children who received 2 prior doses of Comirnaty (Original monovalent) were enrolled to receive a third dose with BNT162b2 (Bivalent Original and BA.4/BA.5). Both children received the study vaccination as assigned and completed the study.
Group 2: A total of 115 children who received 3 prior doses of Comirnaty (Original monovalent) were assigned to receive a fourth dose with BNT162b2 (Bivalent Original and BA.4/BA.5). Of these, 113 children (98.3%) received the study vaccination. Two children (1.7%) withdrew from the study after study vaccination due to withdrawal by participant (n=1) or by parent/guardian (n=1). A total of 111 children (96.5%) completed the study.
Group 3: Nineteen children who received 3 prior doses of Comirnaty (Original monovalent) in Study 1007 were enrolled to receive a fourth dose with BNT162b2 (Bivalent Original and BA.4/BA.5). All children received the study vaccination and completed the study.

6.2.10.1 Populations Enrolled/Analyzed

The populations used for study analyses are defined below. Immunogenicity analyses were conducted on the Evaluable Immunogenicity Population.

- Safety Population: All children who received at least one dose of study intervention. This population was used for all safety analyses.
- Evaluable Immunogenicity Population: Eligible, randomized children who received the study intervention to which they were randomized/assigned, had at least one valid and determinate immunogenicity result from the blood sample collected within the appropriate window (28-42 days after the study dose), and had no other important protocol deviations as determined by the clinician. Primary and secondary immunogenicity endpoints were analyzed in this population.

6.2.10.1.1 Demographics

The demographics of the safety population are presented in Table 20. Groups 1 and 3 demographics are not balanced, likely due to small sample sizes.

Table 20. Study 1048 SSD Demographic Characteristics – Safety Population

Characteristic	Group 1 N[a]=2 n[b] (%)	Group 2 N[a]=113 n[b] (%)	Group 3 N[a]=19 n[b] (%)
Sex	-	-	-
Male	2 (100.0)	57 (50.4)	8 (42.1)
Female	0	56 (49.6)	11 (57.9)
Race	-	-	-
White	2 (100.0)	66 (58.4)	12 (63.2)
Black or African American	0	9 (8.0)	2 (10.5)
Asian	0	13 (11.5)	2 (10.5)
Multiracial	0	22 (20.4)	3 (15.8)
Not reported	0	3 (2.7)	0
Ethnicity	-	-	-

Characteristic	Group 1 N[a]=2 n[b] (%)	Group 2 N[a]=113 n[b] (%)	Group 3 N[a]=19 n[b] (%)
Hispanic/Latino	0	23 (20.4)	0
Non-Hispanic/Non-Latino	2 (100.0)	90 (79.6)	19 (100.0)
Not reported			
Age at vaccination (years)	-	-	-
Mean (SD)	5.0 (0)	8.6 (1.65)	7.8 (1.83)
Median	5.0	9.0	9.0
Min, max	(5, 5)	(5, 11)	(5, 11)
Obese[c]	-	-	-
Yes	Not Reported	10 (8.8)	1 (5.3)
No	Not Reported	103 (91.2)	18 (94.7)
Baseline SARS-CoV-2 status	-	-	-
Positive[d]	Not Reported	66 (58.4)	13 (68.4)
Negative[e]	Not Reported	47 (41.6)	6 (31.6)
Comorbidities[f]	-	-	-
Yes	Not Reported	31 (27.4)	4 (21.1)
No	Not Reported	82 (72.6)	15 (78.9)

Source: Adapted from STN125742/656, c4591048-ssd-interim-mth1-mth6-report-body.pdf, Tables 10 and 12
Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD= standard deviation.

a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Positive N-binding antibody result at the study vaccination visit, positive NAAT result at the study vaccination visit, or medical history of COVID-19.
e. Negative N-binding antibody result at the study vaccination visit, negative NAAT result at the study vaccination visit, and no medical history of COVID-19.
f. Number of participants who had at least 1 high-risk underlying condition, based on MMWR Morb Mortal Wkly Rep. 2020;69(32):1081-8 and CDC high-risk underlying conditions list last updated 09FEB2023 and/or obesity (BMI ≥ 95th percentile).

> ***Reviewer Comment****: Over half of Group 2 (58.4%) had evidence of prior SARS-CoV-2 infection at study baseline, which is expected and consistent with the evolution of "seropositivity" for this age group during the pandemic. This study had comparable percentages of children with at least one condition which put them at increased risk of severe COVID-19 compared with Study 1007 (27.4% and 26.7%, respectively).*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentage of study participants who were overweight or obese are described in Section 6.2.10.1.

6.2.10.1.3 Subject Disposition

See Section 6.2.10.

Protocol Deviations

Groups 1 and 3: No important protocol deviations were reported in these groups.
Group 2: Protocol deviations related to concomitant medications (n=1), inclusion/exclusion criteria (n=1), and investigational product (n=1) were reported for 3 children (2.7%) in the BNT162b2 (Bivalent Original and BA.4/BA.5) group. Two children (1.8%) were excluded from the evaluable immunogenicity population because of important protocol deviations: one related to inclusion/exclusion criteria and the other related to investigational product administration.

6.2.11 Efficacy/Immunogenicity Analyses

Summary

A fourth dose of BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg in children 5 years through 11 years of age demonstrated immune responses against Omicron BA.4/BA.5 that were generally comparable to those observed after a third dose of Comirnaty (Original monovalent) in the same age group.

6.2.11.1 Analyses of Primary Endpoint(s)

Immunogenicity

In the evaluable immunogenicity population with or without evidence of prior infection up to 1 month after study vaccination, regression model-based GMR of Omicron BA.4/BA.5-neutralizing titers for the BNT162b2 (Bivalent Original and BA.4/BA.5) group compared with the Comirnaty (Original monovalent) group was 1.12 (Table 21). Unadjusted GMR was 1.57 (2-sided 95% CI: 1.18, 2.09) (Data not shown).

Table 21. Model-Based Geometric Mean Ratio – C4591048 Substudy D Group 2 (1-Month Post-Dose 4) to C4591007 Phase 2/3 Participants (1-Month Post-Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	C4591048 BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg n[a] GMT[b] (95% CI[b])	C4591007 Comirnaty (Original monovalent) 10 µg n[a] GMT[b] (95% CI[b])	BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg/ Comirnaty (Original monovalent) 10 µg GMR[c] (95% CI[c])
Omicron BA.4/BA.5 NT50 (titer)	101 1836.1 (1593.8, 2115.2)	112 1632.5 (1427.5, 1867.0)	1.12 (0.92, 1.37)

Source: Adapted from STN125742/656, c4591048-ssd-interim-mth1-mth6-report-body.pdf, Table 16
Abbreviations: CI= confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT= nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 90 to 240 days prior to enrollment.
a. n = Number of participants with valid and determinate assay results for the specified assay at both the given dose and the given sampling time point.
b. GMTs and 2-sided CIs were calculated by exponentiating the LSMeans and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
c. GMRs and 2-sided CIs were calculated by exponentiating the difference of LSMeans for the assay and the corresponding CIs based on the same regression model as stated above.

Approximately 53% of BNT162b2 (Bivalent Original and BA.4/BA.5) recipients included in the evaluable immunogenicity population achieved seroresponse to Omicron BA.4/BA.5. The regression model-adjusted difference in percentage of participants with seroresponse between BNT162b2 (Bivalent Original and BA.4/BA.5) recipients and Comirnaty (Original monovalent) recipients was 8.76%, with a lower bound of -2.47% (Table 22). The unadjusted difference in seroresponse percentages was 0.79% (95% CI: -12.57, 14.10) (Data not shown).

Table 22. Adjusted Difference in Percentages of Participants With Seroresponse Between C4591048 Substudy D Group 2 (1-Month Post-Dose 4) and C4591007 Phase 2/3 Participants (1-Month Post-Dose 3) – With or Without Evidence of Infection – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	C4591048 BNT162b2 (Bivalent Original and BA.4/BA.5)10 µg N[a] % (n[b]) (95% CI[c])	C4591007 Comirnaty (Original monovalent) 10 µg N[a] % (n[b]) (95% CI[c])	Difference in Percentage Seroresponse[d] (95% CI[e])
Omicron BA.4/BA.5 NT50 (titer)	101 53.3 (54) (43.3, 63.5)	112 52.7 (59) (43.0, 62.2)	8.76 (-2.47, 19.99)

Source: Adapted from STN125742/656, c4591007-interim-report-body.pdf, Table 17
Abbreviations: CI= confidence interval; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. Note: Substudy D Group 2 includes participants 5-11 years of age who received 3 prior doses of BNT162b2 10 µg 90 to 240 days prior to enrollment.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 4 for C4591048 Substudy D Group 2 and before Dose 3 for C4591007). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. N = number of participants with valid and determinate assay results for the specified assay both before Dose 4 (C4591048)/Dose 3 (C4591007) and at the given dose/sampling time point. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Adjusted difference in proportions based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage (bivalent BNT162b2 [original/Omi BA.4/BA.5] 10 µg - BNT162b2 10 µg). The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
e. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage.

***Reviewer Comment**: The primary descriptive immunogenicity analyses suggest that a fourth dose of BNT162b2 (Bivalent Original and BA.4/BA.5) 10 µg in children 5 years through 11 years of age who had previously received 3 doses of Comirnaty (Original monovalent) elicited immune responses against the Omicron BA.4/BA.5 variant. The regression model-based GMR of 1.12 and the model-adjusted difference of 8.76% in percentage of children with seroresponse indicate that immune responses were generally comparable between the BNT162b2 (Bivalent Original and BA.4/BA.5) recipients and the historical comparator group from Study 1007. However, data interpretability is limited by the non-randomized study design and imbalances in baseline characteristics between groups (i.e., higher pre-vaccination GMTs in the bivalent vaccine group compared with the historical comparator, which may reflect the differences in natural SARS-CoV-2 exposure during different pandemic periods). Children in the comparator group (Study 1007) received their third dose between March and April 2022, shortly after the Omicron BA.1 wave, whereas children in study 1048 SSD had a longer period of potential exposure to multiple Omicron sublineages because they received their fourth dose between September and October 2022.*

The shorter dosing interval in the bivalent group (median 5.5 months vs. 6.5 months) and the 6-month longer period of potential SARS-CoV-2 exposure may have contributed to the higher baseline titers and influenced the magnitude of immune responses. Despite these considerations, the bivalent vaccine demonstrated the ability to stimulate nAb responses against the Omicron BA.4/BA.5 variant.

6.2.11.2 Analyses of Secondary Endpoints

Immunogenicity

GMTs for Omicron BA.4/BA.5 neutralization at 1-month post-vaccination showed an approximately 4.5-fold increase from baseline across all participants from 488.3 (95% CI:

361.9, 658.8) to 2189.9 (95% CI: 1742.8, 2751.7). In participants with evidence of previous SARS-CoV-2 exposure, GMTs increased by 3.5-fold from 1069.2 (95% CI: 782.4, 1461.1) pre-vaccination to 3465.6 (95% CI: 2682.8, 4476.7) post-vaccination. Participants without evidence of previous SARS-CoV-2 exposure, GMTs increased approximately 7-fold from 173.8 (95% CI: 117.3, 257.4) to 1195.8 (95% CI: 850.2, 1681.9).

GMTs for reference strain neutralization, at 1-month post-vaccination also showed a numerical increase from baseline across all participants rising from 2904.0 (95% CI: 2372.6, 3554.5) to 8245.9 (95% CI: 7108.9, 9564.9). In participants with evidence of previous SARS-CoV-2 exposure, GMTs increased from 4198.4 (95% CI: 3342.9, 5272.8) to 9228.4 (95% CI: 7707.0, 11050), while in participants without evidence of previous SARS-CoV-2 exposure, GMTs rose from 1786.4 (95% CI: 1305.0, 2445.5) to 7108.8 (95% CI: 5534.0, 9131.8).

The following data analyses were conducted in the evaluable immunogenicity population with or without evidence of prior infection:

Omicron BA.4/BA.5 Neutralization:

- Overall seroresponse: 53.5% (95% CI: 43.3, 63.5)
- Seroresponse in participants with evidence of previous SARS-CoV-2 exposure: 36.8% (95% CI: 24.4, 50.7)
- Seroresponse in participants without previous SARS-CoV-2 exposure: 75.0% (95% CI: 59.7, 86.8)

Reference Strain Neutralization:

- Overall seroresponse rate: 30.7% (95% CI: 21.9, 40.7)
- Seroresponse in participants with evidence of previous SARS-CoV-2 exposure: 17.5% (95% CI: 8.7, 29.9)
- Seroresponse in participants without previous SARS-CoV-2 exposure: 47.7% (95% CI: 32.5, 63.3)

Reviewer Comment*: The secondary immunogenicity analyses provide additional evidence that the BNT162b2 (Bivalent Original and BA.4/BA.5) vaccine elicited immune responses against both vaccine strains in children 5 years through 11 years of age. The pattern of immune responses was consistent with expected vaccine performance, with higher GMT increases observed in seronegative children compared with baseline seropositive children. This difference likely reflects the lower pre-existing antibody levels in children without evidence of prior infection, allowing for greater relative increases following vaccination.*

Seroresponse rates at 1-month post-vaccination for Omicron BA.4/BA.5 and for the reference strain in children without evidence of prior infection indicated that the majority achieved a ≥4-fold rise in nAb. The numerically lower seroresponse percentages in children with evidence of prior infection are likely consistent with their higher baseline titers, making a 4-fold increase more difficult to achieve.

While *these analyses are descriptive and do not involve formal statistical comparisons with a concurrent control group, the results support the claim that the BNT162b2 (Bivalent Original and BA.4/BA.5) vaccine elicits immune responses against both the Omicron BA.4/BA.5 variant and the Original strain.*

6.2.11.3 Subpopulation Analyses

Immunogenicity endpoints were analyzed by sex in the evaluable immunogenicity population. Results for Omicron BA.4/BA.5 neutralization at 1-month post-vaccination are presented below:

Males (n=48):

- GMT: 2442.8 (95% CI: 1749.9, 3410.2)
- GMFR: 4.0 (95% CI: 3.2, 5.1)
- Seroresponse: 47.9% (95% CI: 33.3, 62.8)

Females (n=54):

- GMT: 1987.2 (95% CI: 1441.3, 2739.8)
- GMFR: 5.0 (95% CI: 3.8, 6.5)
- Seroresponse: 58.5% (95% CI: 44.1, 71.9)

Similar patterns were observed for reference strain neutralization, with comparable immune responses between sexes.

> ***Reviewer Comment:*** *Subpopulation analyses by sex demonstrated generally similar immunogenicity responses following BNT162b2 (Bivalent Original and BA.4/BA.5) vaccination. While males showed numerically higher geometric mean titers, females demonstrated higher geometric mean fold rise and seroresponse percentage. The overlapping confidence intervals for all endpoints suggest that there are no clinically meaningful differences in vaccine immunogenicity between males and females in this pediatric population, but the study was not powered to test this hypothesis. These findings are consistent with previous observations in other age groups and support the use of the bivalent vaccine irrespective of sex. Analyses of other demographic subgroups were limited by small sample sizes in the respective subgroups.*

6.2.11.4 Dropouts and/or Discontinuations

See section 6.1.10.

Group 1: Both children (100%) received the study intervention and completed the study.

Group 2: Of the 115 children assigned to receive *BNT162b2 (Bivalent Original and BA.4/BA.5)*, 113 children (98.3%) received the study intervention. Two children (1.7%) did not receive the study vaccination for reasons not specified in the study records. Following vaccination, 2 children (1.7%) withdrew from the study: one due to withdrawal by participant and one due to withdrawal by parent/guardian. Neither withdrawal was related to adverse events. The overall study completion rate was 96.5% (111/115 participants).

Group 3: All 19 children (100%) received the study intervention and completed the study.

6.2.11.5 Exploratory and Post Hoc Analyses

COVID-19 Case Surveillance

Exploratory analyses evaluated the incidence of COVID-19 cases, disease severity, and potential complications following vaccination with *BNT162b2 (Bivalent Original and BA.4/BA.5)*.

- Groups 1 and 3: No cases of COVID-19 were reported in Group 1. One case of COVID-19 was reported in Group 3, which was identified as XBB.1.5 (Omicron) by strain sequencing. This case met both protocol-defined and CDC-defined criteria for COVID-19 but did not meet criteria for severe disease.
- Group 2: A total of 7 COVID-19 cases were reported during the follow-up period. Six cases (85.7%) met both protocol-defined and CDC-defined criteria for COVID-19. No cases met the criteria for severe COVID-19 as defined by either protocol or CDC criteria.

Strain Sequencing Results
Among the determinate and quantifiable sequence results for COVID-19 cases (n=7 in Group 2), all cases were caused by Omicron subvariants:

- 4 cases of XBB.1.5 (Omicron)
- 1 case of XBB.1.5.35 (Omicron)
- 1 case of BQ.1 (Omicron)
- 1 case of BQ.1.1.4 (Omicron)

No cases of severe COVID-19 or MIS-C were reported in any of the study groups throughout the follow-up period.

6.2.12 Safety Analyses

6.2.12.1 Methods

See Section 6.2.7.

6.2.12.2 Overview of Adverse Events

Unsolicited non-serious AEs were reported in 4.4% of Group 2 participants (Table 23). One participant (0.9%) reported lymphadenopathy, which was assessed as related to the investigational vaccine by the investigator. All other AEs were assessed as unrelated. The median follow-up time after study vaccination was 6.3 months (range 1.1, 6.8 months).

Table 23. Overview of AEs – Number (%) of Participants Reporting at Least 1 Adverse Event From Study Vaccination to 1 Month After The Study Vaccination – Safety Population

Event	Group 1 N[a]=2 n[b] (%)	Group 2 N[a]=113 n[b] (%)	Group 3 N[a]=19 n[b] (%)
Solicited injection site reaction within 7 days	1 (50.0)	74 (65.5)	13 (68.4)
Solicited systemic reaction within 7 days	0	58 (51.3)	12 (63.2)
Unsolicited non-serious AE within 1 month	0	5 (4.4)	3 (15.8)
SAEs	--	--	--
up to 6 months (or unblinding)	0	0	0
Deaths	0	0	0

Source: Adapted from STN125742/656, c4591048-ssd-interim-mth1-mth6-report-body.pdf, Appendix 16.2.7.2.1, Table 20, Supplemental Table 14.25, Supplemental Table 14.32, Supplemental Table 14.39, Supplemental Table 14.42, Table 24
Abbreviations: SAEs = serious adverse events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.

Solicited Adverse Reactions:
Local Reactions
Pain at the injection site was the most commonly reported local reaction within 7 days of vaccination. Among participants in Group 2 (N=111), 64.0% (n=71) reported pain, with 45.0% (n=50) reporting mild pain and 18.9% (n=21) moderate pain. Similarly, in Group 3 (N=19), 68.4% (n=13) reported pain, with mostly mild (52.6%; n=10) and 15.8% (n=3) moderate cases. One of the 2 participants in Group 1 (50%) experienced mild pain.

In Group 2, redness was reported by 9 participants (7.2%; mild for 4.5% and moderate for 2.7%), swelling by 5 participants (4.5%l moderate for 3.6% and mild for 0.9%). Both redness

and swelling were reported by 10.5% (2/19) of Group 3 participants; all cases were mild. Neither redness nor swelling were reported in the two Group 1 participants.

The local reactions had a median onset of 1 to 2 days post-vaccination across all groups. The median duration of local reactogenicity was 1.5 to 2 days across all groups (range: 1-8 days). No severe or Grade 4 local reactions were reported in any group. Female participants reported more local reactions than males (76.8% vs 56.4% for any local reaction). Pain at the injection site was reported by 73.2% of females compared with 54.5% of males.

Systemic Reactions
In Group 2 (N=111), the most commonly reported systemic event, reported by 40.5% (n=45) of participants was fatigue. Of these, 23.4% (n=26) experienced mild fatigue, 16.2% (n=18) moderate, and 0.9% (n=1) severe. Headache was the second most commonly reported event, affecting 25.2% (n=28) of participants, with 18.0% (n=20) reporting mild, 6.3% (n=7) moderate, and 0.9% (n=1) severe headaches. Other systemic events in Group 2 included new or worsened muscle pain (13.5%, n=15), chills (9.0%, n=10), and new or worsened joint pain (9.0%, n=10). Fever (≥38.0°C) was reported in 4.5% (n=5) of participants, with 1.8% (n=2) experiencing fever >38.9°C to 40.0°C. Vomiting and diarrhea occurred in 3.6% (n=4) of participants.

In Group 3 (N=19), fatigue was also the most commonly reported systemic event, occurring in 57.9% (n=11) of participants. Of these, 36.8% (n=7) reported mild fatigue, 15.8% (n=3) moderate, and 5.3% (n=1) severe. Headache was reported by 36.8% (n=7) of participants, with 26.3% (n=5) experiencing mild and 10.5% (n=2) moderate headaches. Fever (≥38.0°C) was observed in 10.5% (n=2) participants, with one case (5.3%) of fever >38.9°C to 40.0°C. New or worsened muscle pain affected 21.1% (n=4) of participants, while chills and new or worsened joint pain each affected 10.5% (n=2). The onset of systemic events was within a few days of vaccination; median onset ranged from 2 to 4 days. The duration of these events had a median ranging from 1.0 to 3.0 days, with the longest individual event duration lasting up to 20 days.

No systemic events were reported in Group 1 (N=2).

Use of antipyretic or pain medication was reported by 23.4% (26/111) of participants in Group 2 and 31.6% (6/19) in Group 3.

Male participants experienced more systemic events than females (58.2% vs 46.4% for any systemic event). Baseline SARS-CoV-2 positive participants experienced more systemic events compared with baseline negative participants (55.4% vs 47.8% for any systemic event).

No life-threatening (Grade 4) systemic events were reported in any group.

Immediate AEs:
No participant in any group experienced an immediate AE within 30 minutes of study vaccination.

Unsolicited Adverse Events
Group 1 did not report any AEs

In Group 2, 5 participants (4.4%) reported at least one unsolicited adverse event. One participant (0.9%) reported an AE (lymphadenopathy) that was determined to be related to vaccination and one participant (0.9%) reported a severe AE of influenza.

In Group 3, 3 participants (15.8%) reported at least one unsolicited adverse event within the first month after vaccination. None of the AEs were considered by the investigator to be related to vaccination.

> ***Reviewer Comment****: No serious adverse events were reported in any group throughout the study period. The safety data from this study suggest that the BNT162b2 (Bivalent Original and BA.4/BA.5) vaccine has a safety profile with reactogenicity and adverse event patterns similar to those observed with Comirnaty (Original monovalent). The study size limits the ability to detect very rare adverse events.*

Surveillance of COVID-19 Cases
See Section 6.2.11.5.

6.2.12.3 Deaths

There were no deaths reported in any of the study groups.

6.2.12.4 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events reported in any of the study groups.

6.2.12.5 Adverse Events of Special Interest (AESI)

In Group 2, three participants underwent cardiac evaluation visit within 4 weeks after vaccination. No cases of protocol-specified AESI, myocarditis/pericarditis, were reported through 6 months after study vaccination.

> ***Reviewer Comment****: Two participants who underwent cardiac evaluation had symptoms consistent with a non cardiac etiology or received an alternative diagnosis. The third participant had an additional workup including an EKG and troponin testing that were within reference range and interpreted as unremarkable.*

6.2.12.6 Clinical Test Results

Clinical laboratory evaluations related to safety were not performed in this study.

6.2.12.7 Dropouts and/or Discontinuations

There were no discontinuations/withdrawals due to AEs reported through 6 months after study vaccination.

6.2.13 Study Summary and Conclusions

Immunogenicity
The primary immunogenicity analyses in Group 2 demonstrated that a fourth dose of *BNT162b2 (Bivalent Original and BA.4/BA.5)* elicited immune responses against the Omicron BA.4/BA.5 variant based on the following endpoints:

- Geometric Mean Ratio of 1.12 (95% CI: 0.92, 1.37) for Omicron BA.4/BA.5-neutralizing titers at 1-month post-Dose 4 compared with historical controls from Study 1007 (1-month post-Dose 3 of original vaccine), suggesting comparable immune responses.

- Seroresponse: 53.5% (95% CI: 43.3, 63.5) of participants achieved seroresponse to Omicron BA.4/BA.5 at 1-month post-Dose 4.
- Reference Strain-specific nAb titers against demonstrated GMTs comparable to those observed with the original vaccine in historical controls.
- Baseline SARS-CoV-2 Status: Participants with evidence of prior SARS-CoV-2 infection showed higher baseline and post-vaccination GMTs but lower geometric mean fold rises compared with baseline seronegative participants.

Safety

The reactogenicity profile was generally mild to moderate and transient, consistent with that observed for Comirnaty (Original monovalent) in this age group. Local reactions, primarily pain at the injection site, were reported by the majority of participants but were mostly mild in severity. Systemic reactions, predominantly fatigue and headache, were also generally mild to moderate. Most reactions had onset within 1-2 days post-vaccination and resolved within a median of 2 days (range: 1-20 days). No Grade 4 reactogenicity events were reported across any study group.

In Group 2 (N=113), 4.4% of participants reported unsolicited adverse events within the first month, most of which were mild to moderate in severity. Only one event (lymphadenopathy) was assessed by the investigator as related to the study intervention. Seven cases of COVID-19 were reported post-vaccination in Group 2, all caused by Omicron subvariants (XBB.1.5, XBB.1.5.35, BQ.1, BQ.1.1.4) and none meeting criteria for severe disease.

No confirmed cases of myocarditis or pericarditis were reported despite active monitoring for these events. No cases of MIS-C were reported in any study group. There were no SAEs assessed as related to the study intervention and no deaths were reported throughout the study period.

> ***Reviewer Comment:*** *The totality of safety and immunogenicity data from Substudy D supports the use of BNT162b2 (Bivalent Original and BA.4/BA.5) as an additional dose in children 5 years through 11 years of age who have previously received Comirnaty (Original monovalent). The single dose elicited immune responses against both the Omicron BA.4/BA.5 variant and the Original strain while maintaining a safety profile consistent with Comirnaty (Original monovalent).*

6.3 C4591048 Substudy E (Study 1048 SSE)

NCT05543616
"A Master Phase 1/2/3 Protocol to Investigate the Safety, Tolerability, and Immunogenicity of Variant-Adapted BNT162b2 RNA-Based Vaccine Candidate(s) in Healthy Children."

Study 1048 E was a Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) in children 5 years through 11 years of age who were COVID-19 vaccine-naïve.

Study 1048 E initiated enrollment October 31, 2023, and the analyses presented were based on a last patient last visit date of October 10, 2024.

6.3.1 Objectives (Primary, Secondary)

Primary Safety: To describe the safety and tolerability profile of prophylactic Comirnaty (Monovalent XBB.1.5) given as a single dose in COVID-19 vaccine-naïve children 5 years through 11 years of age.

Endpoints: Solicited local reactions for up to 7 days following study vaccination (pain at the injection site, redness, and swelling); solicited systemic events for up to 7 days following study vaccination (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain); AEs from the study vaccination through 1 month after the study vaccination; SAEs from the study vaccination through 6 months after the study vaccination

Primary Immunogenicity: To immunobridge the Omicron XBB.1.5 immune response elicited by a single dose of Comirnaty (Monovalent XBB.1.5) between COVID-19 vaccine-naïve children 5 years through 11 years of age who received a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) and vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A.

Endpoints:

- GMR of SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at 1 month after study vaccination in COVID-19 vaccine–naïve children 5 years through 11 years of age who received a single dose of Comirnaty (Monovalent XBB.1.5) to neutralizing titers at 1 month after study vaccination in Study C4591054 compared with Substudy A vaccine-experienced participants ≥12 years of age.
- The difference in percentage of participants with seroresponse to Omicron XBB.1.5 at 1 month after study vaccination between COVID19 vaccine–naïve children 5 years through 11 years of age who received a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) and vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 – Substudy A.

Secondary Immunogenicity: To describe the immune response elicited by Comirnaty (Monovalent XBB.1.5) given as a single 10-µg dose in in COVID-19 vaccine-naïve children 5 years through 11 years of age.

Endpoints: from participants complying with the key protocol criteria (evaluable participants):

- GMTs at baseline and 1 month after the study vaccination.
- GMFR from baseline and 1 month after the study vaccination.
- Percentages of participants with seroresponse at baseline and 1 month after the study vaccination.

6.3.2 Design Overview

Phase 2/3 open-label study to evaluate the safety, tolerability, and immunogenicity of a single 10-ug dose of Comirnaty (Monovalent XBB.1.5) in COVID-19 vaccine-naïve children 5 years through 11 years of age. Approximately 300 children were planned to be enrolled. The primary objectives were: 1) to describe the safety and tolerability profile, and 2) to immunobridge the Omicron XBB.1.5 immune response in children 5 years through 11 years of age to that elicited in vaccine-experienced participants ≥12 years who received a 30-µg dose of Comirnaty (Monovalent XBB.1.5) in C4591054 Substudy A.

6.3.3 Population

Key Inclusion Criteria: Male or female individuals 5 years through 11 years of age at the time of enrollment, who are healthy or who have preexisting disease not requiring significant change in therapy or hospitalization during the six weeks before enrollment.

Key Exclusion Criteria: Individuals who have received medications intended to prevent COVID-19, have a diagnosis of MIS-C, have a history of severe adverse and/or allergic reaction to any component of the study intervention, have known or suspected immunodeficiency, have autoimmune disease (excepting stable type 1 diabetes and hypothyroidism), have a bleeding diathesis, have a history of myocarditis or pericarditis, have other medical or psychiatric conditions that would increase study participation risk, or are pregnant or breastfeeding.

Additional exclusion criteria include previous vaccination with any COVID-19 vaccine, receipt of systemic immunosuppressants within 60 days before enrollment, receipt of blood products, monoclonal antibodies, or immunoglobulins within 60-90 days before study intervention (depending on type of product), planned receipt of blood products, monoclonals, or immunoglobulins, and receipt of other study interventions from 28 days prior to study entry through 28 days after study intervention dose.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Intervention Name: Comirnaty (Monovalent XBB.1.5)
Unit Dose Strength: 100 µg/mL
Dosage Level: 10 µg
Route of Administration: IM injection
Dosing Regimen: Single dose

6.3.5 Directions for Use

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

6.3.6 Sites and Centers

This study was conducted at 30 sites in the US, South Africa, and Brazil.

6.3.7 Surveillance/Monitoring

An independent External Data Monitoring Committee (EDMC) reviewed safety data routinely and on an *ad hoc* basis. The recommendations made by the EDMC were forwarded to the authorized Applicant personnel for review and final decision. The safety parameters included reactogenicity e-diary reports of local reactions and systemic events (including fever) and use of antipyretic medication that occurred in the 7 days after administration of the study intervention.

Safety Monitoring

- Immediate AEs during 30 minutes post study vaccine
- Local reactions for up to 7 days following study vaccine (pain at the injection site, redness, and swelling)
- Systemic events for up to 7 days following study vaccine (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, new or worsened joint pain)
- AEs for 1 month after the study vaccine
- SAEs for 6 months after the study vaccine
- AESI for 6 months after the study vaccine. Myocarditis and pericarditis were designated as AESIs, and protocol-specified procedures were to be followed for any participant reporting acute chest pain, shortness of breath, palpitations, or other symptoms potentially indicative of myocarditis/pericarditis within 6 weeks after vaccination. Any occurrence was also reported as AE or SAE per above procedures.

6.3.8 Endpoints and Criteria for Study Success

See section 6.3.1.

6.3.9 Statistical Considerations & Statistical Analysis Plan

See section 6.3.1 for study objectives.

Sample size calculations: Study enrollment aimed for approximately 300 children. A similar number of participants ≥12 years of age from Study C4591054 Substudy A who received a single dose of Comirnaty (Monovalent XBB.1.5) 30-µg were selected to evaluate the primary immunogenicity objective. Assuming a 25% non-evaluable rate, approximately 225 evaluable participants would be needed in each vaccine group for immunogenicity evaluation. Each hypothesis test was performed at a 1-sided alpha level of 0.025. For GMR, using a 1.5-fold margin, if the true GMR is 1.05, 225 evaluable participants in each arm were estimated to provide 89.3% power to declare noninferiority. If the true GMR is 1.0, the study had approximately 82% power to declare noninferiority. For comparison based on seroresponse rate differences, using a 10% margin, if the seroresponse rate was 70% in both comparator groups, the study had 64.0% power to demonstrate noninferiority.

Immunogenicity analyses: The primary immunogenicity objective was to immunobridge the Omicron XBB.1.5 immune response (i.e., GMR of neutralizing titers and difference in seroresponse rates) between COVID-19 vaccine-naïve children 5 years through 11 years who received a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) and vaccine-experienced participants ≥12 years who received a single 30-µg dose in Study C4591054 Substudy A. The immunobridging success criteria were 1) GMR: Lower limit of 2-sided 95% CI > 0.67 and point estimate ≥ 0.8, and 2) seroresponse percentage difference: Lower limit of 2-sided 95% CI > -10%. Analyses were conducted in the evaluable immunogenicity population and all-available immunogenicity population.

Efficacy objectives: The study did not have formal efficacy objectives. However, it included exploratory objectives to describe COVID-19 and severe COVID-19 cases, as well as MIS-C cases.

Safety analyses: 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.

6.3.10 Study Population and Disposition

Study period: The study was initiated October 31, 2023, and the last patient last visit date of October 10, 2024.

Disposition: The study enrolled 310 healthy children aged 5 years through 11 years who were COVID-19 vaccine-naïve; all received study vaccine. Most participants (92.6%) completed the study. Twenty-three participants (7.4%) withdrew from the study, most commonly due to loss during follow-up (n=17), followed by protocol deviations (n=5).

6.3.10.1 Populations Enrolled/Analyzed

Analysis sets included:

- Enrolled: all participants who have a signed ICD.
- Assigned: all participants who are assigned a randomization number in the IRT system

- Safety: all participants who received at least one dose of the study intervention
- Evaluable immunogenicity: all eligible participants who receive the study intervention to which they are assigned, have at least 1 valid immunogenicity result from the blood sample collected within 28-42 days after the study vaccination, and have no other important protocol deviations.
- All-available immunogenicity: all assigned participants who receive at least 1 dose of the study intervention with at least 1 valid immunogenicity result after vaccination.

6.3.10.1.1 Demographics

Approximately half of the safety population were female (52.9%) (Table 24). Most had evidence of prior SARS-CoV-2 infection at study baseline (98.7%). The median age at study vaccination was 7.0 years. Most participants were from the United States (69.0%) followed by South Africa (21.0%), Brazil (9.4%), and Puerto Rico (0.6%). Approximately 35% had at least one comorbidity known to increase risk of severe COVID-19 disease. The median follow-up time after study vaccination was 6.4 months, and most participants (92.3%) had a follow-up time ≥6 months (data not shown).

Table 24. Demographic Characteristics - Substudy E - Safety Population

Characteristic	Comirnaty (Monovalent XBB.1.5) 10 µg (N[a]=310) n[b] (%)
Sex	--
Male	146 (47.1)
Female	164 (52.9)
Race	--
White	128 (41.3)
Black or African American	164 (52.9)
American Indian or Alaska Native	1 (0.3)
Asian	6 (1.9)
Multiracial	10 (3.2)
Not reported	1 (0.3)
Ethnicity	--
Hispanic/Latino	162 (52.3)
Non-Hispanic/non-Latino	148 (47.7)
Country	--
Brazil	29 (9.4)
Puerto Rico	2 (0.6)
South Africa	65 (21.0)
United States	214 (69.0)
Age at the study vaccination (years)	--
Mean (SD)	7.4 (1.98)
Median	7.0
Min, max	(5, 11)
Obese[c]	--
Yes	78 (25.2)
No	232 (74.8)
Baseline SARS-CoV-2 status	--
Positive[d]	306 (98.7)
Negative[e]	3 (1.0)
Missing	1 (0.3)
Comorbidities[f]	--

Characteristic	Comirnaty (Monovalent XBB.1.5) 10 µg (N[a]=310) n[b] (%)
Yes	109 (35.2)
No	201 (64.8)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 6
Abbreviations: MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/data/zscore/bmiagerev.xls.
d. Positive N-binding antibody result at the study vaccination visit, positive NAAT result at the study vaccination visit, or medical history of COVID-19.
e. Negative N-binding antibody result at the study vaccination visit, negative NAAT result at the study vaccination visit, and no medical history of COVID-19.
f. Number of participants who had at least 1 high-risk underlying condition, based on MMWR. 2020;69(32):1081-8 and CDC high-risk underlying conditions list last updated 09FEB2023 and/or obesity (BMI ≥ 95th percentile).

Demographic characteristics of the evaluable immunogenicity populations from Study 1048 SSE (Table 25) were generally similar to those in the safety population. Participants in the Study 1048 SSE group had higher percentages of Black or African American and Hispanic/Latino participants compared with the Study C4591054 group, due in part to enrollment of Study 1048 SSE in both South Africa and Brazil.

Table 25. Demographic Characteristics - C4591048 Substudy E and C4591054 Substudy A Participants - Evaluable Immunogenicity Population

Characteristic	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg (N[a]=285) n[b] (%)	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg (N[a]=302) n[b] (%)
Sex	--	--
Male	132 (46.3)	126 (41.7)
Female	153 (53.7)	176 (58.3)
Race	--	--
White	117 (41.1)	239 (79.1)
Black or African American	151 (53.0)	39 (12.9)
American Indian or Alaska Native	1 (0.4)	0
Asian	6 (2.1)	15 (5.0)
Native Hawaiian or other Pacific Islander	0	1 (0.3)
Multiracial	9 (3.2)	7 (2.3)
Not reported	1 (0.4)	0
Unknown	0	1 (0.3)
Ethnicity	--	--
Hispanic/Latino	152 (53.3)	58 (19.2)
Non-Hispanic/non-Latino	133 (46.7)	242 (80.1)
Not reported	0	2 (0.7)
Country	--	--
Brazil	28 (9.8)	0
Puerto Rico	2 (0.7)	0
South Africa	61 (21.4)	0
United States	194 (68.1)	302 (100.0)

Characteristic	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg (N[a]=285) n[b] (%)	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg (N[a]=302) n[b] (%)
Age (years) at study vaccination	--	--
Mean (SD)	7.4 (1.97)	51.7 (18.77)
Median	7.0	53.5
Min, max	(5, 11)	(12, 82)
Obese[c]	--	--
Yes	67 (23.5)	110 (36.4)
No	218 (76.5)	192 (63.6)
Baseline SARS-CoV-2 status	--	--
Positive[d]	282 (98.9)	300 (99.3)
Negative[e]	3 (1.1)	2 (0.7)
Comorbidities/ Underlying high risk conditions[f]	--	--
Yes	96 (33.7)	221 (73.2)
No	189 (66.3)	81 (26.8)
Time from last dose of mRNA COVID-19 vaccine[g] (received prior to the study) to the study vaccination (months[h])	--	--
N	NA	302
Mean (SD)	NA	10.2 (1.75)
Median	NA	10.7
Min, max	NA	(5.5, 12.9)
≥5 to <7 Months	NA	19 (6.3)
≥7 to <9 Months	NA	59 (19.5)
≥9 to ≤12 Months	NA	193 (63.9)
>12 Months	NA	31 (10.3)
Time from last dose of mRNA COVID-19 vaccine[g] (received prior to the study) to the study vaccination (days)	--	--
N	NA	302
Mean (SD)	NA	285.8 (49.08)
Median	NA	300.0
Min, max	NA	(154, 360)
<150 Days	NA	0
≥150 Days[i]	NA	302 (100.0)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 7
Abbreviations: NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; NA = not applicable; SD = standard deviation.
a. N = number of participants in the specified group. These values are the denominators for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. For participants 5 through 15 years of age, obesity is defined as a BMI at or above the 95th percentile from the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/data/zscore/bmiagerev.xls. Since the participant's age is only collected in years (C4591054 SSA only) and the BMI values in the CDC growth charts are only presented by age in months, the minimum 95th percentile value for that age was chosen for the obesity criteria. For participants ≥16 years of age obesity is defined as a BMI at or above 30.0 kg/m2.
d. Positive N-binding antibody result at the study vaccination visit, positive NAAT result at the study vaccination visit, or medical history of COVID-19.
e. Negative N-binding antibody result at the study vaccination visit, negative NAAT result at the study vaccination visit, and no medical history of COVID-19.
f. Number of participants who had at least 1 high-risk underlying condition, based on MMWR. 2020;69(32):1081-8 and CDC high-risk underlying conditions list last updated 09FEB2023 and/or obesity (BMI ≥95th percentile) for C4591048 SSE, and participants with at least 1 CDC defined high-risk conditions, based on NEJM 2025;392:2484-2486, obesity, and/or age 65 years or older for C4591054 SSA.

g. The inclusion criteria for Study C4591054 SSA required the participant to have received at least 3 prior doses of a US-authorized mRNA COVID-19 vaccine with the most recent dose being a US-authorized Omicron BA.4/BA.5-adapted bivalent vaccine at least 150 days before study vaccination.
h. Month was calculated as 28 days.
i. Protocol-specified time frame.

***Reviewer Comment**: Demographic characteristics were mostly balanced across the safety and immunogenicity populations. There were several notable differences between the Study 1048 SSE and C4591054 Substudy A populations – in particular age, race, ethnicity, presence of comorbidities, and country of origin. For age, the median age for participants from Study 1048 SSE was 7.0 years compared with 53.5 years for participants from C4591054 Substudy A. These differences could have implications for comparison of the immune responses.*

More than a third (35%) of the safety population (33.7% of the immunogenicity population) had a comorbidity associated with an increased risk of severe COVID-19 disease. Nearly all (98.7%) of participants had baseline evidence of SARS-CoV-2 exposure (positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19). These demographics likely reflect the current demographics of the US population.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentages of participants who were obese and who had comorbidities are noted in Section 6.3.10.1.1.

6.3.10.1.3 Subject Disposition

See section 6.3.10.

Protocol Deviations (PD)
Important PDs were reported for two participants. One participant did not meet inclusion criterion 2 (parent/guardian willing to comply with study procedures). One participant received an investigational product that was deemed not suitable for use.

6.3.11 Efficacy/Immunogenicity Analyses

Summary
Study 1048 SSE successfully met all primary immunobridging endpoints, demonstrating COVID-19 vaccine-naïve children 5 years through 11 years of age achieved noninferior immune responses with a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) compared with vaccine-experienced adults who received a 30-µg dose.

6.3.11.1 Analyses of Primary Endpoint(s)

Primary Immunogenicity
In the evaluable immunogenicity population, the model-based GMR of Omicron XBB.1.5-neutralizing titers for the Comirnaty (Monovalent XBB.1.5) 10-µg group to the Comirnaty (Monovalent XBB.1.5) 30-µg group was 1.81 (2-sided 95% CI: 1.51, 2.16) (Table 26). The alternative model-based GMR (excluding post-baseline infection status from the model) was identical to the model-based GMR (data not shown). Immunobridging success was declared since the lower limit of the 2-sided 95% CI for the GMR was greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR was ≥0.8. Results for participants in the all-available immunogenicity population (data not shown) were similar to those from the evaluable immunogenicity population.

Table 26. Model-Based Geometric Mean Ratio - C4591048 Substudy E to C4591054 Substudy A Participants at 1 Month After the Study Vaccination - Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg n[a] GMT[b] (95% CI[b])	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg n[a] GMT[b] (95% CI[b])	C4591048 5-11 Years/ C4591054 ≥12 Years GMR[c] (95% CI[c])
Omicron XBB.1.5 - NT50 (titer)	285 6569.3 (5781.6, 7464.3)	300 3635.9 (3210.5, 4117.6)	1.81 (1.51, 2.16)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 9
Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; NT50 = 50% neutralizing titer; Omi = Omicron; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. n = Number of participants with valid and determinate assay results for the specified assay at both baseline and at the given sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the LSMeans and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LSMeans for the assay (C4591048 ≥5 to <12 Years - C4591054 ≥12 Years) and the corresponding CIs based on the same regression model as stated above.

In the evaluable immunogenicity population, 88.8% of participants in the Study 1048 SSE Comirnaty (Monovalent XBB.1.5) 10-µg group and 77.0% of participants in the C4591054 Comirnaty (Monovalent XBB.1.5) 30-µg group achieved seroresponse to Omicron XBB.1.5 (Table 27). The unadjusted difference in percentages of seroresponse was 11.77% (95% CI: 5.74, 17.84) (Data not shown). Immunobridging success was declared since the lower limit of the 2-sided 95% CI for the adjusted difference in percentages of seroresponse was >-10%. Results for participants in the all-available immunogenicity population (data not shown) were similar to those from the evaluable immunogenicity population.

Table 27. Adjusted Difference in Percentages of Participants With Seroresponse Between C4591048 Substudy E and C4591054 Substudy A Participants at 1 Month After the Study Vaccination - Evaluable Immunogenicity Population

SARS-CoV-2 Neutralization Assay	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg N[a] % (n[b]) (95% CI[c])	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg N[a] % (n[b]) (95% CI[c])	Percent (%) Difference[d] (95% CI[e])
Omicron XBB.1.5 - NT50 (titer)	285 88.8 (253) (84.5, 92.2)	300 77.0 (231) (71.8, 81.6)	8.97 (3.91, 14.02)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 10
Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; Omi = Omicron; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. N = number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given sampling time point. This value is the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given sampling time point.
c. Exact 2-sided 95% CI, based on the Clopper and Pearson method.
d. Adjusted difference in proportions based on the Miettinen and Nurminen method stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage (C4591048 ≥5 to <12 Years - C4591054 ≥12 Years). The median of baseline neutralizing titers was calculated based on the pooled data in 2 comparator groups.
e. 2-Sided 95% CI, based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralizing titer category (< median, ≥ median), expressed as a percentage.

***Reviewer Comment**: Immunobridging analyses met both prespecified success criteria for GMR and difference in percentage of seroresponse. The results demonstrate that COVID-19 vaccine-naïve children 5 years through 11 years of age achieved an immune response with a single 10-µg dose that was noninferior to vaccine-experienced adults receiving a licensed 30-µg dose. This finding supports the appropriateness of the single-dose regimen at a lower dose for this pediatric population.*

6.3.11.2 Analyses of Secondary Endpoints

Secondary Immunogenicity

Geometric Mean Titers

Among both Study 1048 SSE participants and C4591054 participants in the evaluable immunogenicity population, GMTs against the Omicron XBB.1.5 variant increased by approximately 30 and 11-fold, respectively, 1 month after study vaccination from baseline (Table 28). Results for participants by subgroup followed a similar trend as those for the overall evaluable immunogenicity population (Table 28). Results for participants in the all-available immunogenicity population (data not shown) were similar to the evaluable immunogenicity population.

Table 28. Geometric Mean Titers (SARS-CoV-2 neutralization Assay Omicron XBB.1.5 - NT50 titer), by Subgroup - C4591048 Substudy E and C4591054 Substudy A Participants - Evaluable Immunogenicity Population

Subgroup	Sampling Time Point[a]	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg n[b] GMT[c] (95% CI[c])	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg n[b] GMT[c] (95% CI[c])
Overall	Prevax	285 195.0 (163.2, 233.0)	300 355.1 (301.5, 418.2)
Overall	1 Month	285 5930.5 (5283.8, 6656.4)	302 4006.4 (3438.3, 4668.4)
Sex - Male	Prevax	132 215.3 (167.2, 277.2)	126 313.6 (244.7, 401.7)
Sex - Male	1 Month	132 6062.0 (5074.9, 7241.0)	126 3620.6 (2805.6, 4672.4)
Sex - Female	Prevax	153 179.1 (139.3, 230.2)	174 388.6 (312.3, 483.5)
Sex - Female	1 Month	153 5819.4 (4995.5, 6779.2)	176 4307.7 (3562.7, 5208.4)
Race – White	Prevax	117 187.5 (141.5, 248.5)	237 329.2 (275.4, 393.5)
Race – White	1 Month	117 7587.7 (6409.7, 8982.3)	239 3877.7 (3267.5, 4602.0)

Subgroup	Sampling Time Point[a]	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg n[b] GMT[c] (95% CI[c])	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg n[b] GMT[c] (95% CI[c])
Race – Black or African American	Prevax	151 210.8 (164.7, 269.9)	39 440.7 (256.6, 757.0)
Race – Black or African American	1 Month	151 4838.5 (4116.0, 5687.9)	39 4357.4 (2579.5, 7360.9)
Race – Other	Prevax	17 127.9 (64.6, 253.3)	24 528.4 (287.7, 970.5)
Race – Other	1 Month	17 6630.7 (4048.2, 10860.8)	24 4838.4 (3320.6, 7049.9)
Ethnicity – Hispanic/ Latino	Prevax	152 187.7 (147.3, 239.2)	58 278.1 (196.2, 394.3)
Ethnicity – Hispanic/ Latino	1 Month	152 6325.9 (5351.5, 7477.7)	58 2870.3 (1866.0, 4415.3)
Ethnicity – Non Hispanic/ Latino	Prevax	133 203.7 (156.3, 265.5)	240 369.7 (307.3, 444.7)
Ethnicity – Non Hispanic/ Latino	1 Month	133 5508.8 (4701.5, 6454.8)	242 4319.9 (3679.4, 5072.0)
Comorbidities - Yes	Prevax	96 187.9 (139.3, 253.5)	220 328.7 (269.5, 401.1)
Comorbidities - Yes	1 Month	96 6806.2 (5537.8, 8365.0)	221 3875.5 (3214.6, 4672.4)
Comorbidities – No	Prevax	189 198.7 (159.0, 248.3)	80 438.9 (332.3, 579.8)
Comorbidities – No	1 Month	189 5529.9 (4810.4, 6356.9)	81 4386.5 (3383.7, 5686.5)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 14.19
Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS- CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: All others = American Indian or Alaska Native, Asian, Native Hawaiian, or other Pacific Islander, Multiracial, Not reported and Unknown race categories.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
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.

GMFR

GMFRs from before study vaccination to 1 month after vaccination against Omicron XBB.1.5 were higher in the Study 1048 SSE participants who received Comirnaty (Monovalent XBB.1.5) 10 µg compared with the C4591054 participants who received Comirnaty (Monovalent XBB.1.5)

30 µg (data not shown). Results for the all-available immunogenicity population were similar to those for the evaluable immunogenicity population.

Seroresponse
One month following vaccination, seroresponse rates against Omicron XBB.1.5 were higher in the Study 1048 SSE participants who received Comirnaty (Monovalent XBB.1.5) 10 µg compared with C4591054 participants who received Comirnaty (Monovalent XBB.1.5) 30 µg (Table 29). Seroresponse results for subgroups followed a similar trend as those for overall evaluable immunogenicity population.

Table 29. Number (%) of Participants With Seroresponse at 1 Month After the Study Vaccination, by Subgroup - C4591048 Substudy E and C4591054 Substudy A Participants - Evaluable Immunogenicity Population

Subgroup	Sampling Time Point[a]	C4591048 5-11 Years Comirnaty (Monovalent XBB.1.5) 10 µg N[b] % (n)[c] (95% CI[d])	C4591054 ≥12 Years Comirnaty (Monovalent XBB.1.5) 30 µg N[b] % (n)[c] (95% CI[d])
Overall	1 Month	285 88.8 (253) (84.5, 92.2)	302 77.0 (231) (71.8, 81.6)
Sex – Male	1 Month	132 91.7 (121) (85.6, 95.8)	126 77.0 (97) (68.6, 84.0)
Sex – Female	1 Month	153 86.3 (132) (79.8, 91.3)	176 77.0 (134) (70.0, 83.0)
Race – White	1 Month	117 94.9 (111) (89.2, 98.1)	239 79.3 (188) (73.6, 84.3)
Race – Black or African American	1 Month	151 82.8 (125) (75.8, 88.4)	39 69.2 (27) (52.4, 83.0)
Race – Other	1 Month	17 100 (17) (80.5, 100)	24 66.7 (16) (44.7, 84.4)
Ethnicity – Hispanic/ Latino	1 Month	152 91.4 (139) (85.8, 95.4)	58 74.1 (43) (61.0, 84.7)
Ethnicity – Non Hispanic/ Latino	1 Month	133 85.7 (114) (78.6, 91.2)	242 78.3 (188) (72.6, 83.4)
Comorbidities – Yes	1 Month	96 91.7 (88) (84.2, 96.3)	220 76.4 (168) (70.2, 81.8)
Comorbidities – No	1 Month	189 87.3 (165) (81.7, 91.7)	80 78.8 (63) (68.2, 87.1)

Source: Adapted from STN125742/656, c4591048-sse-interim-mth6-report-body.pdf, Table 14.23
Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline. If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: All others = American Indian or Alaska Native, Asian, Native Hawaiian, or other Pacific Islander, Multiracial, Not reported and Unknown race categories.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay both baseline and at the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided 95% CI, based on the Clopper and Pearson method.

6.3.11.3 Subpopulation Analyses

Immunogenicity data were presented by subgroup (sex, race, ethnicity, and comorbidity) when possible (See Section 6.3.11.2).

6.3.11.4 Dropouts and/or Discontinuations

See Section 6.3.10.

6.3.11.5 Exploratory and Post Hoc Analyses

Four cases (1.3%) of COVID-19 were reported after study vaccination; causative SARS-CoV-2 strains were identified as JN.1.9 (n=1), KP.2.3 (n=1), and unknown (n=2) due to insufficient quantities. All 4 cases met both protocol-defined and CDC-defined criteria for COVID-19 (Appendix B). None met the severe criteria per the protocol and CDC definitions (Appendix B). No cases of MIS-C were reported after study vaccination.

6.3.12 Safety Analyses

6.3.12.1 Methods

See section 6.3.7.

6.3.12.2 Overview of Adverse Events

Among the 310 children in the safety population, 11 (3.5%) reported any AEs through 1 month following vaccination (Table 30). SAEs of acute gastroenteritis and seizure were separately reported in 2 participants (0.6%), with seizure reported as related to vaccination. Three participants (1.0%) reported 4 severe AEs, including hyperglycemia and seizure in 1 participant, non-cardiac chest pain in 1 participant and acute gastroenteritis in 1 participant. No life-threatening AEs, withdrawals due to AEs, or deaths were reported. Eighteen (5.8%) participants reported any AEs from study vaccination through 6 months after study vaccination. One additional SAE of acute gastroenteritis with dehydration and 1 additional severe AE of acute gastroenteritis with dehydration were reported through 6 months after vaccination.

Table 30. Overview of AEs – Number (%) of Participants Reporting at Least 1 Adverse Event From Vaccination to 6 months After – Safety Population

Event	N=310 n (%)
Solicited injection site reaction within 7 days	135 (44.9)
Solicited systemic adverse reaction within 7 days	92 (30.5)
Unsolicited non-serious AE within 1 month	11 (3.5)
SAEs	--
up to 6 months	3 (1.0)
Deaths	0

Source: FDA created table.
Abbreviations: SAEs = serious adverse events.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any adverse event," n = the number of participants reporting at least 1 occurrence of any adverse event.

Solicited Adverse Reactions:
Local Reactions:
Pain at the injection site was the most frequently reported local reaction within 7 days after study vaccination (43%), followed by swelling (9%), and redness (6%). Most local reactions were mild to moderate in severity. Severe swelling was reported in 1 participant (0.3%) within 7 days after study vaccination, which decreased in severity to moderate by Day 4 (Appendix 16.2.7.2). No Grade 4 local reactions were reported. The median onset for all local reactions was 1 to 2 days after study vaccination, and median duration was 1 to 1.5 days after onset (range: 1 to 26 days).

Systemic Reactions:
Fatigue, headache, and muscle pain were the most frequently reported systemic events within 7 days after study vaccination (ranging between 10% and 15%), followed by diarrhea (7%), chills (6%), fever and joint pain (5% for both), and vomiting (4%). Most systemic events were mild or moderate in severity. Severe fever (>40°C) was reported in 1 participant (0.3%), severe fatigue in 2 participants (0.7%), and severe headache in 1 participant (0.3%) within 7 days after the study vaccination. No Grade 4 systemic events were reported. The median onset for all systemic events was 2 to 5 days after study vaccination, and all events resolved within a median duration of 1 to 2 days after onset (range: 1 to 16 days).

Immediate AEs:
No immediate AEs were reported after study vaccination.

Unsolicited Adverse Events:
Eleven participants (3.5%) reported unsolicited AEs within 1 month of vaccination. Through 6 months after study vaccination, 4 participants (1.3%) had AEs considered related to the study vaccine, namely upper abdominal pain, decreased appetite, and dizziness in one participant (n=1); seizure (n=1), diarrhea (n=1), and non-cardiac chest pain (n=1). Four participants reported severe AEs: hyperglycemia and seizure in 1 participant (n=1), non-cardiac chest pain (n=1), acute gastroenteritis (n=1), and acute gastroenteritis with dehydration (n=1). No life-threatening AEs were reported from study vaccination through 6 months after study vaccination.

6.3.12.3 Deaths

No deaths were reported from study vaccination through 6 months after study vaccination.

6.3.12.4 Nonfatal Serious Adverse Events

Three participants (1%) reported SAEs from study vaccination through 6 months after study vaccination: gastroenteritis (n=2) and seizure (n=1) (Table 14). The seizure occurred 13 days after vaccination in an 8-year-old African American male with no past medical history who began to convulse while sleeping after candy consumption. There was no preceding illness or event, the seizure lasted 1-2 minutes and resolved without intervention. The participant was transported to an emergency department (ED) by emergency medical services (EMS). Notable results from the work-up was a normal brain MRI and electroencephalogram showing left temporal spikes. The participant also has an AE for “hyperglycemia” as participant’s guardian reported an elevated blood glucose measurement on EMS arrival; however, his blood glucose was within normal limits in the ED with no glucose lowering intervention. The participant was discharged from the ED with a prescription for levetiracetam, which he remained on through study completion. No further episodes of seizure occurred while in study follow-up. The participant was scheduled for follow-up with pediatric neurology but did not attend the

appointment. The seizure was considered related to the vaccination by the investigator, but the Applicant did not concur with the assessment.

> ***Reviewer Comment****: Following detailed independent review of the SAEs, this reviewer concurs with the assessment of relatedness with one exception of the event of seizure. This reviewer agrees with the Applicant but not the investigator that the seizure was unlikely to be related to the investigational product for the following reasons: it occurred 13 days after the vaccination, potential alternative etiology (hyperglycemia of 283 mg/dL), the diagnosis was never confirmed with Neurology (participant missed follow-up appointment), self-controlled case series studies have found no association between COVID-19 vaccination and new onset seizure (Ko et. al. 2025), and independent reviews of Vaccine Adverse Events Reporting System Data have not identified a signal for an association of seizure with COVID-19 vaccination (Liu et al. 2025).*

6.3.12.5 Adverse Events of Special Interest (AESI)

Myocarditis/pericarditis is a protocol-specified AESI; no cases were reported in the 310 children 5 years through 11 years of age from study vaccination through 6-months post-vaccination. Two participants underwent cardiac evaluation visits for protocol-specified potential myocarditis/ pericarditis symptoms.

- One participant reported chest pain, with headache and pyrexia, 5 days after vaccination. At the cardiac evaluation visit (5 days post vaccination), the participant had a normal troponin I, and an abnormal ECG finding of repolarization anomaly, specifically “alteration of repolarization in V1 and V5.” At the protocol required cardiology evaluation (17 days post-vaccination), the participant had a normal ECG and a normal echocardiogram; the chest pain was attributed as “non-cardiac chest pain,” with 2 days duration.
- One participant reported shortness of breath 10 days after vaccination. No protocol required assessments were performed because the site physicians did not deem the symptoms to be of cardiac etiology; the participant had a positive SARS-CoV-2 NAAT from the nasal swab collected during the concurrent COVID-19 illness surveillance visit.
- One participant (0.3%) reported an AE of interest (seizure) during the study (noted in section 6.3.12.4). No other AEs of interest were identified through 6 months after study vaccination.

6.3.12.6 Clinical Test Results

Clinical laboratory evaluations related to safety were not performed in this study.

6.3.12.7 Dropouts and/or Discontinuations

There were no discontinuations due to AEs reported for participants throughout the study.

6.3.13 Study Summary and Conclusions

Immunogenicity

One-month post-dose immunogenicity data from 285 COVID-19 vaccine-naïve children 5 years through 11 years of age who received a single dose of 10 µg of Comirnaty (Monovalent XBB.1.5) demonstrated immunobridging success against Omicron XBB.1.5.

- Immunobridging success was demonstrated for both model-based GMR and difference in percentage of participants with seroresponse between Study 1048 SSE vaccine-naïve children 5 years through 11 years of age who received 10-µg Comirnaty (Monovalent XBB.1.5) and Study C4591054 vaccine-experienced participants ≥12 years of age who received 30-µg Comirnaty (Monovalent XBB.1.5).

- Lower GMTs at pre-vaccination and higher GMTs at 1 month after vaccination were observed in Study 1048 SSE children compared with Study C4591054 participants, including in each subgroup.
- Higher GMFRs and seroresponse percentages were observed in Study 1048 SSE children compared with participants from Study C4591054, including in each subgroup.

Safety

A single dose of Comirnaty (Monovalent XBB.1.5) was generally well tolerated in the safety population (n=310) through 6 months after study vaccination; the adverse event profile was consistent with what was previously reported with Comirnaty (Original monovalent). No new safety signals were identified. Reactogenicity events within 7 days after study vaccination were mostly mild or moderate. The AE profile through 6 months after study vaccination was consistent with what has been previously described for Comirnaty (Original monovalent). The incidence of AEs and SAEs was low. No life-threatening AEs or AEs leading to withdrawal were reported. One AE of interest (seizure) was reported during the substudy. No cases of myocarditis/ pericarditis were reported. No new or concerning safety findings were noted in participants through 6 months after study vaccination. Four cases of COVID-19 were reported after study vaccination. Based on the safety data through 6 months after a single 10 µg dose, Comirnaty (Monovalent XBB.1.5) is considered safe and tolerable in this population.

7. INTEGRATED OVERVIEW OF EFFICACY

Two studies (1007 and 1048 SSE) provided effectiveness data for Comirnaty in children 5 years through 11 years of age. Study 1007 was conducted during a period when many participants had little serologic evidence of prior SARS-CoV-2 infection and received multiple doses of the vaccine to meet efficacy outcomes. Study 1048 SSE was conducted during a period when most children older than 5 years of age had serologic evidence of previous COVID-19. Additionally, the study designs differed by vaccine administered [i.e., Comirnaty (Original monovalent) vs. Comirnaty (Monovalent XBB.1.5)], age, and geographic location. Therefore, an integrated summary of efficacy may be informative. The totality of effectiveness data submitted in this sBLA supports the use of a single dose of Comirnaty in children 5 years of age and older, irrespective of prior COVID-19 vaccination status.

8. INTEGRATED OVERVIEW OF SAFETY

The safety of Comirnaty was based on 3 studies (Studies 1007, 1048 SSD, and 1048 SSE). Study 1007 was conducted during the time when many individuals had no evidence of previous COVID-19 exposure and received more than one dose in the vaccine regimen. Studies 1048 SSD and SSE were conducted during a period when most individuals over the age of 5 years had evidence of previous COVID-19 exposure. Additionally, the study designs differed by vaccine administered [i.e., Comirnaty (Original monovalent) vs. BNT162b2 (Bivalent Original and BA.4/BA.5) vs. Comirnaty (Monovalent XBB.1.5)], age, and geographic location. Therefore, an integrated summary of safety was not considered to be informative. The totality of data on safety supports the use of a single dose of Comirnaty in children 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were excluded from enrollment in the clinical studies submitted to this sBLA.

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 PREA Considerations

The pediatric assessment in individuals 5 years through 11 years of age was based on three studies. For COVID-19 vaccine-experienced individuals, a single dose of Comirnaty including Comirnaty (2025-2026 Formula) is supported by Study 1007 (safety) and Study 1048 SSD (safety); please see Section 6.1 and Section 6.2 for clinical review of the respective studies. For COVID-19 vaccine-naïve individuals, the effectiveness of a single dose of Comirnaty, including Comirnaty (2025-2026 Formula), in vaccinated individuals 5 years through 11 years of age is inferred and supported by Study 1048 SSE (safety and immunogenicity). This submission fulfills PREA PMR #1 (STN 125742/686) and PREA PMR #3 (STN 125742/686) and Comirnaty will be indicated for use in individuals 5 years of age and older.

9.1.4 Immunocompromised Patients

This sBLA does not include data from clinical studies specifically addressing whether the vaccine is safe and effective for use in immunocompromised individuals. Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to Comirnaty.

9.1.5 Geriatric Use

Adults 65 years of age and older were excluded from enrollment in the clinical studies submitted to this pediatric sBLA. Please refer to Section 8.5 of USPI for information regarding use of Comirnaty in older adults.

10. CONCLUSIONS

The clinical data support approval of Comirnaty for active immunization to prevent COVID-19 in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination status. Data from the three studies included in this sBLA support the safety and effectiveness of a single 10-µg dose of Comirnaty (including the 2025-2026 Formula), in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination status, for prevention of COVID-19 caused by SARS-CoV-2. The safety and effectiveness data accrued for Comirnaty (Original monovalent), BNT162b2 (Bivalent Original and BA.4/BA.5) and Comirnaty (Monovalent XBB.1.5) are pertinent because these vaccines are manufactured using a similar process as Comirnaty, including Comirnaty (2025-2026 Formula).

Effectiveness in Children 5 years through 11 years
A single 10-µg dose of Comirnaty, including the 2025-2026 Formula, is effective in children 5 years through 11 years of age irrespective of previous COVID-19 vaccination status. The

following data from the submitted clinical trial database support the effectiveness of Comirnaty in this age group:

- Noninferior immune response following 2 doses of Comirnaty (Original monovalent) as compared with the response following 2 doses of Comirnaty (Original monovalent) in young adults (16 years through 25 years old) in whom clinical efficacy was demonstrated in Study C4591001 and efficacy of Comirnaty (Original monovalent) against confirmed COVID-19 occurring from 7 days post-Dose 2 to prior to Dose 3 during the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection (Study 1007, reviewed in Section 6.1).
- Noninferior immune response following a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) in COVID-19 vaccine-naïve children compared with immune response in vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A (Study 1048 SSE, reviewed in Section 6.3).
- Descriptive increase in immune response 1 month after vaccination among COVID-19 vaccine-experienced individuals who received an additional single dose of Comirnaty (Original monovalent) (Study 1007, reviewed in Section 6.1).
- Descriptive comparison of the immune response among COVID-19 vaccine-experienced individuals who received a single dose of BNT162b2 (Bivalent Original and BA.4/BA.5) compared with individuals Study 1007 participants who received 3 doses of Comirnaty (Original monovalent) (Study 1048 SSD, reviewed in Section 6.1).

As described above in Study 1048 SSE, a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) in COVID-19 vaccine-naïve children with likely prior exposure to SARS-CoV-2 elicited a noninferior immune response compared with the immune response in vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A. Earlier in the pandemic, when a 2-dose series was evaluated in vaccine-naïve school-age children in Study 1007 with 90% baseline SARS-CoV-2 negative (see Table 5), robust immune responses were elicited with that dosing posology. Based on current seroprevalence data, over 96% of children 5 years through 11 years (CDC 2025d) have antibodies against SARS-CoV-2 from either vaccination or infection, lending support to the current single-dose use approach.

Safety in Children 5 years through 11 years

Data provided in this sBLA support the safety of a single 10-µg dose of Comirnaty in children 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status. The following data support the safety of Comirnaty in this age group:

- If COVID-19 vaccine-naïve:
  - Single dose (10 µg) of Comirnaty (Monovalent XBB.1.5) in children 5 years through 11 years of age with evidence of prior SARS-CoV-2 infection (Study 1048 SSE). [Reviewed in Section 6.3].
  - 2-dose series (10 µg each) of Comirnaty (Original monovalent) in children 5 years through 11 years (Study 1007). [Reviewed in Section 6.1].
- If previously COVID-19 vaccinated:
  - Additional single dose (10 µg) of Comirnaty (Original monovalent) in children 5 years through 11 years of age (Study 1007 Booster part). [Reviewed in Section 6.1].
  - Additional single dose (10 µg) of a BNT162b2 (Bivalent Original and BA.4/BA.5) in children 5 years through 11 years of age (Study 1048 SSD). [Reviewed in Section 6.2].

In the clinical studies submitted to this sBLA, local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and the mean duration was 1 to 2.6 days (range: 1 to 119). Across the clinical studies, there were no SAEs considered to be possibly related to this vaccine. There were no new safety concerns considering the current Comirnaty (Original monovalent) USPI. Based on review of available data, the clinical safety profile of the Comirnaty platform was not adversely impacted by strain changes to the encoded mRNA Spike protein.

Postmarketing data with authorized or approved mRNA COVID-19 vaccines demonstrate increased risk of myocarditis and pericarditis, particularly within the first week following the second vaccination, with the highest observed risk in males 12 years through 24 years of age. The risk of myocarditis is appropriately described in USPI (Section 5 Warnings and Precautions, Section 5.2 Myocarditis and Pericarditis, Section 6.2 Postmarketing Experience). There were no cases of myocarditis or pericarditis in the studies submitted to this sBLA.

The safety and effectiveness of Comirnaty (Original monovalent), BNT162b2 (Bivalent Original and BA.4/BA.5), and Comirnaty (Monovalent XBB.1.5) are relevant to Comirnaty (2025-2026 Formula) because these vaccines are manufactured using a similar process.

Based on the totality of the evidence and the risk-benefit considerations described in Section 11 below, this clinical reviewer concludes that the data submitted in this sBLA, along with available postmarketing data, support approval of Comirnaty for the indication of active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 years through 11 years of age as a single dose irrespective of prior COVID-19 vaccination status.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 31. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 is associated with significant morbidity, mortality (over 7 million deaths worldwide to date) and long-term sequelae among survivors. In the U.S., COVID-19 has been responsible for 1.2 million deaths to date with a cumulative COVID-19-associated hospitalization rate of 77.8 per 100,000 people for the 2024-2025 season, as of June 28, 2025, with the highest hospitalization rates in individuals over 65 years of age (317.4 per 100,000 people). • SARS-CoV-2 continues to evolve, particularly in the spike protein's receptor-binding domain. Successive waves of variants, including Delta, Omicron BA.1, BA.5, XBB.1.5, and JN.1, have demonstrated increased transmissibility and, in some cases, greater ability to evade immunity from prior infection or vaccination. The trajectory of SARS-CoV-2 continues to remain unpredictable, including the potential emergence of variants with greater immune escape or virulence. • A large percentage of the U.S. population has developed immunity through vaccination, prior infection, or a combination thereof. While this has contributed to reduced rates of severe disease, it complicates assessments of vaccine effectiveness over time. The durability of immunity and the impact of waning immune protection on future disease burden are not fully known. • Updated vaccine formulae continue to show relative vaccine effectiveness (i.e., added benefit) in a population with high prevalence of seropositivity.	• COVID-19 continues to pose a substantial public health threat, both from acute infections and long-term complications. COVID-19 burden, including hospitalizations and deaths, are high among individuals over 65 years of age and in infants and young children. • Vaccination remains a cornerstone of the public health response, with updated formulae improving effectiveness against currently circulating variants. • Due to ongoing SARS-CoV-2 evolution and despite widespread seropositivity, it is important to continue surveillance and to maintain flexibility in vaccine development and public health planning.
Unmet Medical Need	• COVID-19 remains a serious illness, particularly for older adults, young infants and children, and individuals with underlying health conditions. While many individuals recover within 1-2 weeks, some experience prolonged symptoms or develop post-acute sequelae known as Long COVID, contributing to long-term morbidity. Children may also experience a serious medical condition associated with COVID-19 called Multisystem Inflammatory Syndrome in Children (MIS-C). The ability of current treatments to prevent Long COVID and MIS-C remains unclear. • Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; these therapeutics are more effective when taken soon after disease onset and are generally more effective against mild to moderate COVID-19. The age of the patient and the presence or absence of immunity from natural infection and prior COVID-19 immunization may also affect the benefit of using these treatments for COVID-19. • Currently, four COVID-19 vaccines (Spikevax, mNexspike, Comirnaty, and Nuvaxovid) have received FDA approval for prevention of COVID-19, but while Pfizer-BioNTech COVID-19 Vaccine, is authorized for use in children as young as 6	• Although treatments exist for those infected with SARS-CoV-2, they are generally not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including Long COVID and MIS-C. • Vaccines provide important protection from COVID-19. • There is only one COVID-19 vaccine recently approved (July 2025) for infants and children less than 12 years of age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	months of age under EUA, there is only one COVID-19 vaccine that was recently approved for children under 12 years of age (July 2025).	

Clinical Benefit	• Effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination is based on:
	  • Immunogenicity of a single dose (10 µg) of Comirnaty (XBB.1.5 monovalent formulation) in COVID-19 vaccine-naïve children 5 years through 11 years of age with evidence of prior SARS-CoV-2 as evaluated in Study 1048 SSE
	  • Immunogenicity of an additional single dose (10 µg) of Comirnaty (Original monovalent) in previously vaccinated individuals 5 years through 11 years of age as evaluated in Study 1007 Booster Phase
	  • Immunogenicity of an additional single dose (10 µg) of a bivalent vaccine (Original and Omicron BA.1) in previously vaccinated individuals 5 years through 11 years of age as evaluated in Study 1048 SSD
	• The original 2-dose series evaluation in COVID-19 vaccine-naïve individuals is analogous to a single dose in vaccine-naïve individuals with evidence of previous SARS-CoV-2 exposure. Thus, effectiveness of a single dose (10 µg) of Comirnaty in children 5 years through 11 years of age irrespective of prior COVID-19 vaccination is also supported by Study 1007 data including:
	  • Immunogenicity following 2 doses of Comirnaty (Original) as compared with the nAb responses following 2 doses of BNT162b2 in young adults (18 years through 25 years old) for whom clinical efficacy was demonstrated in Study C4591001
	  • Efficacy of Comirnaty against confirmed COVID-19 occurring from 7 days post-Dose 2 to prior to Dose 3 during the blinded follow-up period in participants without evidence of past SARS-CoV-2 infection.
	• All studies listed above met their primary pre-specified success criteria.
	• Uncertainties in clinical benefit include: precise estimate of relative vaccine efficacy in children less than 12 years of age, effectiveness against severe disease, durability of protection beyond 6-12 months, effectiveness in preventing asymptomatic infection or transmission, and effectiveness of future formulae (i.e., updated variant compositions) against future circulating variants.
		• The evidence for clinical benefit of a single dose (10 µg) of Comirnaty meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status, to prevent COVID-19 caused by SARS-CoV-2.

Risk	• The most frequently reported adverse reactions were solicited local adverse reactions of injection site pain and axillary swelling or tenderness and systemic adverse reactions of fatigue, headache, and new or worsened muscle pain. These reactions were generally mild to moderate in severity, occurred within 1-3 days after vaccination, and resolved quickly. Unsolicited AEs within 1-month post-vaccination were generally consistent with solicitated ARs or common childhood illnesses. There were no SAEs reported in the studies submitted to this sBLA which were assessed as related to Comirnaty. • No cases of vaccine-related myocarditis, pericarditis, or anaphylaxis were observed in the studies submitted to this sBLA. This is consistent with the observed epidemiology of vaccine-related myocarditis and pericarditis, which have not been	• In the clinical studies, across individuals 5 years through 11 years of age, and following one or two vaccinations, local and/or systemic solicited adverse reactions following vaccination were generally mild to moderate and of short duration (mean 1-3 days). Relevant related adverse events have been added to the USPI as described. There were no other new safety concerns identified in study data reviewed in this application which were not already identified in the current Comirnaty (Original monovalent) USPI.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	shown to occur at higher frequency in children under 12 years of age. However, these events remain recognized potential risks for the vaccine class.	
Risk Management	• Labeling for Comirnaty describes the common and uncommon (but potentially serious) risks associated with the vaccine, which are unchanged based on the data reviewed in this sBLA for children 5 years through 11 years of age, as no new safety signals were identified. The Comirnaty prescribing information includes warning statements for severe allergic reactions and myocarditis/pericarditis. • Postmarketing monitoring for AEs using both passive and active surveillance systems will be used to assess for emergence of any new safety concerns.	• Risk mitigation strategies for Comirnaty in individuals 5 years of age and older are unchanged based on the review of this sBLA and 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.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of Comirnaty in preventing symptomatic COVID-19 in children 5 years through 11 years of age is favorable compared with potential risks associated with vaccination. Study 1007 was a large, multipart Phase 3 study which met its pre-specified primary endpoints, demonstrating noninferior nAb responses against SARS-CoV-2 strains encoded for in the vaccine compared with nAb responses following a 2-dose series in young adults generated from the pivotal efficacy study (Study C4591001) on which initial authorization and licensure of Comirnaty was based. Study 1048 SSD met the primary effectiveness objective to descriptively compare the nAb response to Omicron BA.4/BA.5 between participants who received 3 prior doses of Comirnaty (Original monovalent) and participants who received BNT162b2 (Bivalent Original and BA.4/BA.5) as a fourth dose and Study 1007 participants who received 3 doses of Comirnaty (Original monovalent). Study 1048 SSE met its primary effectiveness objective to demonstrate noninferiority of Omicron XBB.1.5 immune response elicited by a single dose of Comirnaty (Monovalent XBB.1.5) between COVID-19 vaccine-naïve participants who received a single 10-µg dose of Comirnaty (Monovalent XBB.1.5) and vaccine-experienced participants ≥12 years of age who received a single 30-µg dose of Comirnaty (Monovalent XBB.1.5) in Study C4591054 Substudy A. The safety of Comirnaty in the pediatric population is adequately described in the product's prescribing information. The Applicant's routine pharmacovigilance and the additional ongoing PMR studies to assess for the risk of myocarditis and pericarditis after vaccination are adequate for monitoring of AEs postmarketing.

11.3 Discussion of Regulatory Options

The data submitted with the BLA efficacy supplement indicate the safety and effectiveness of Comirnaty meet the statutory requirements to support its use in individuals 5 years through 11 years of age, irrespective of prior COVID-19 vaccination status, to prevent COVID-19 caused by SARS-CoV-2. 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

This clinical reviewer recommends approval of Comirnaty (2025-2026 Formula) for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 5 years through 11 years of age and older, administered as a single dose irrespective of prior COVID-19 vaccination status.

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.

11.6 Recommendations on Postmarketing Actions

The Applicant has committed to conduct the following postmarketing studies:

Study 1: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (COVID-19 Vaccine, mRNA) (2025-2026 Formula) in participants 65 years of age and older and

in participants 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

Final Protocol Submission: August 30, 2025

Study Initiation: September 30, 2025

Interim Results: February 28, 2026

Study Completion Date: July 31, 2026

Final Report Submission: September 30, 2026

Study 3: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (COVID-19 Vaccine, mRNA) (2025-2026 Formula) in participants 5 years through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

Final Protocol Submission: August 30, 2025

Study Initiation: September 30, 2025

Interim Results: February 28, 2026

Study Completion Date: July 31, 2026

Final Report Submission: September 30, 2026

12 APPENDIX A. ADVERSE EVENTS OF SPECIAL INTEREST

The Applicant identified myocarditis and pericarditis, defined by the Brighton Collaboration, as the AESI for their protocols reviewed in this sBLA. The definitions are available at the following website and were last accessed on July 21, 2025: https://brightoncollaboration.us/myocarditis-case-definition-update/

13 APPENDIX B. COVID-19 CASE DEFINITIONS

The Applicant's definitions used in Study C4591007:

Confirmed COVID-19:
First definition: Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggers a potential COVID-19 illness visit:

- 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, as defined by ≥3 loose stools/day
- Vomiting

Second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html), but does not trigger a potential COVID-19 illness visit unless in the opinion of the PI deemed necessary:

- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea or abdominal pain
- Lethargy

SARS-CoV-2–related severe case:
Confirmed COVID-19 and presence of at least 1 of the following triggers a potential COVID-19 illness visit:

- Clinical signs at rest indicative of severe systemic illness (RR (breaths/min) and HR (beats/min) as shown in the Table below; SpO2 ≤92% on room air or >50% FiO2 to maintain ≥92%, or PaO2/FiO2 <300 mm Hg)

Table 32. Age-Specific Respiratory Rate and Heart Rate Thresholds for SARS-CoV-2-Related Severe Cases

Participant Age	RR	HR
4 to < 6 years	>29	>131
6 to <8 years	>27	>123
8 to < 12 years	>25	>115

- Respiratory failure (defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock or cardiac failure:
  - SBP (mm Hg):
  - <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years; or requiring vasoactive drugs to maintain BP in the normal range;
- Significant acute renal failure: Serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine
- Significant GI/hepatic failure: Total bilirubin ≥4 mg/dL or ALT 2 times ULN for age
- Significant neurological dysfunction: Glasgow Coma Scale score ≤11 or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline
- Admission to an ICU
- Death.

Second definition, which may be updated as more is learned about COVID-19, will include the following additional outcomes defined by the CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions.html):

- Hospitalization
- Admission to the ICU
- Intubation or mechanical ventilation

- Death

Confirmed MIS-C definition (per the CDC MIS-C case definition):

- An individual <21 years of age presenting with fever (≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours); **AND**
- Laboratory evidence of inflammation (based on local laboratory ranges) including, but not limited to, 1 or more of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin; **AND**
- Evidence of clinically severe illness requiring hospitalization (definition as noted above for severe disease), with multisystem (≥2) organ involvement:
    - Cardiac (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia);
    - Renal (eg, acute kidney injury);
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
    - Hematologic (eg, elevated D-dimers, thrombophilia, or thrombocytopenia)
    - GI/hepatic (eg, elevated bilirubin, elevated liver enzymes, or diarrhea)
    - Dermatologic (eg, rash, mucocutaneous lesions)
    - Neurological (eg, CVA, aseptic meningitis, encephalopathy); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; **OR** COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: Positive N-binding antibody result in a participant with a prior negative N-binding antibody result;
- Current or recent exposure is established by SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms; all positive RT-PCR cases confirmed by the central laboratory will undergo BioFire testing.
- Past serological and virological status is established by SARS-CoV-2 PCR or history of reported COVID-19.